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ANNALS OF INTERNAL MEDICINE

VOLUME 26 FEBRUARY, 1947 NUMBER 2

MEDICINE IN THE EUROPEAN THEATER OF OPERATIONS *

By WILLIAM S. MIDDLETON, F.A.C.P., *Madison, Wisconsin*

THE Professional Services Division of the Chief Surgeon's Office in the European Theater of Operations did not spring into functional maturity upon the declaration of war by the German Reich. A comprehensive plan of consultation service had been projected in the American Expeditionary Forces in World War I. Armistice came before all of its weaknesses had been remedied. In World War II a group of distinguished specialists constituted the Army Medical Directorate Consultants' Committee to the Director General of the Royal Army Medical Corps in London, whereas two able clinicians and a pathologist acted as professional advisers to the Director General of the Royal Canadian Army Medical Corps. With these experiences ready at hand the basic plan for medical supervision of the American forces in the European Theater was early adopted; nor was it materially altered in the three years of operations.

On the staff of the Chief Surgeon and administratively next in responsibility for the medical care of the sick and wounded was the Director of Professional Services. Under him were the Chief Consultant in Medicine and the Chief Consultant in Surgery. Turning immediately to the Medical Consultation Service (figure 1), Senior Consultants in the medical sub-specialties carried the continuity of responsibility. Neuropsychiatry, dermatology, infectious diseases, cardiology and tuberculosis were here represented. Neuropsychiatry is a heavy service in military medicine. With the delegation of the care of venereal diseases to medicine, dermatology assumed the supervision of this added clinical load and became a close runner-up to neuropsychiatry. Hence, the Senior Consultants in Neuropsychiatry and

* Presented at the 27th Annual Session, American College of Physicians, Philadelphia, May 13, 1946.

From the Department of Medicine, University of Wisconsin Medical School.

The figures herein quoted were graciously afforded by Col. Joseph H. McNinch, Director of the Historical Division, Surgeon General's Office. They are still tentative. Col. John E. Gordon, Chief of Preventive Medicine Division, Chief Surgeon's Office, European Theater of Operations, gave further invaluable data.

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Dermatology, with full-time tasks, were stationed at Headquarters. The Senior Consultants in Infectious Diseases, Cardiology and Tuberculosis, on the other hand, were primarily concerned with policy formation in their restricted areas of medical activity. They were selected from qualified chiefs of the medical services of fixed hospitals and continued to act in the dual capacity of chief of the service and Senior Consultant to the Theater in the medical subspecialty. With the growth of the Theater these Senior Consultants were severally advanced to the status of Regional Consultants and then to Base Section Consultants. They still retained their subsidiary, but

FIG. 1. Plan of organization—Medical consultation service in the European theater of operations.

important, rôle of advisers to the Theater in their respective spheres. Additional Base Section Consultants were required. In a few instances their tasks were so onerous as to preclude further clinical duties; but where there was a restricted area of activities, a qualified chief of a medical service was selected. With the evolution of hospital center program, appropriate leaders were selected from among the chiefs of the medical services of the component units to act in a second capacity as Medical Consultant to the group. Instead of over 200 scattered units, from a professional as well as an administrative standpoint, prompt contact could be made at 15 points of command (seven hospital centers in the United Kingdom, eight on the Continent).

The Medical Consultants in the Armies (five) constituted the ultimate link in the continuity of professional communication. Through these Army consultants medical policies were implemented in combat elements and a unity of medical approach assured through all echelons.

Although research is not a primary function of the Medical Department in the active Theater of Operations, it was deemed expedient to organize the continuing flow of medical information and clinical inquiry in a central office. Accordingly, the post of Director of Medical Research was established to coordinate such efforts. A file of research projects was maintained. All proposals requiring financial support or the transfer of personnel were investigated and their merit rated upon the grounds of military bearing, solubility in a short time and availability of the necessary materials and personnel. Upon such advice the Chief Surgeon could then act with clear insight. The Director of Medical Research continued in his primary responsibility as Commanding Officer of the 1st Medical General Laboratory.

In the schematic outline of the Medical Consultation Service in European Theater channels of professional communication have been drawn. Official channels were used in all matters relating to military or tactical procedure; but with the support of the Chief Surgeon, Major General Paul R. Hawley, direct communication in purely professional details was encouraged. By this expedient, operating through the simplified system of decentralized control, information regarding disease trends, therapeutic innovations and similar medical data might be promptly disseminated. Nor was the advantage unilateral; frequently the initiating source of valuable information was an isolated field unit or mobile hospital. The Chief Consultant in Medicine held periodic Conferences of the Chiefs of Medical Services. This important integrating agency was later decentralized to Base and Hospital Center levels. Monthly meetings of the Professional Services Division under the Chief Surgeon supplemented weekly informal gatherings of the Consultants at Headquarters. To these sessions all Senior Consultants and Base Section Consultants were invited.

The Medical Consultation Service sought to offer the highest possible medical service to every American soldier. Perhaps the most important element in rendering such a service effective was the confidence of the Chief Surgeon in its mission. Under his leadership the Professional Services Division became the focal point of the Medical Department in the European Theater. The closest rapport existed between the Medical Consultation Service and the Preventive Medicine Division of the Chief Surgeon's Office. The propinquity and the interlocking interests of these elements rendered immediate intelligence in all matters pertaining to the health of the command possible. Their functions must always be interdependent. The Senior Consultant in Infectious Diseases, the Chief of Laboratories and the Chief of the Preventive Medicine Division constituted the Advisory Committee on Infectious Diseases which coördinated the mutual effort in that area.

Obviously to insure the best medical service under all conditions there must be the optimal ultilization of the available personnel. All new hospitals assigned to the Zone of Communications were visited upon arrival in the Theater. By personal interviews and staff conferences evaluations of the unit as a whole and of its component members were made. (In 1944 the Chief Consultant in Medicine personally visited and interviewed the officers of the Medical Sections of 108 general and 11 station hospitals from the Zone of Interior and four general and two station hospitals from MTOUSA.) Marked discrepancies in numbers and qualifications became apparent as the reserve of medical officers in the United States was exhausted. Fortunately the affiliated hospitals that had first arrived in the Theater and those transferred from MTOUSA afforded a wealth of qualified and tried internists. From this reservoir 58 new chiefs of medical services were made; but the dilution was becoming precarious by 1945. On the other hand tours of duty in the Armies disclosed occasional instances of inadequately utilized skills. On the initiation of the Army Surgeon, the consultant would make the recommendation for appropriate exchange. The Personnel Division depended implicitly upon the Professional Services Division for advice in these directions. To their everlasting credit it should be stated that never was a recommendation for the movement of a medical officer in the interest of better care for the soldier made by the Medical Consultants without prompt compliance.

Although more directly involved in matters relating to personnel than certain other functions of the Chief Surgeon's Office the consultants were apprised of the tactical situation. The Finance and Supply Division advised with Professional Services upon drugs, supplies and equipment dealing with the immediate care of patients. In accepting drugs of foreign origin the Chief Consultant in Medicine conferred with British representatives to establish standards of equivalence. The counsel of the consultants was sought in arranging Tables of Basic Allowance for chemicals and drugs for all operations. Policies of hospitalization, evacuation and redeployment were established after conference with the affected consultant. All directives for therapy emanated from this Division.

The interest of the Medical Consultants was fundamentally clinical. In the early days of the Theater the Chief Consultant in Medicine made monthly clinical rounds in each hospital in the United Kingdom. This recurring contact with the practice of the area gave an excellent opportunity for coordination and ultimately paid unanticipated dividends in a knowledge of the most promising young clinicians who were later required to strengthen medical services in the understaffed new units. With the ever increasing troop lift and hospitalization program (total beds 259, 725, of which 183,550 were in fixed hospitals) the ideal of monthly clinical rounds was met by decentralization. Instead of a single individual for the Theater, a Base Section or a Hospital Center Consultant made periodic professional visits in the area of his responsibility.

For the advancement of medical service the several reports to the Medical Records Office were made available to the Consultants. Aside from the indication of the immediate disease incidence probably their most useful purpose was met in the Weekly Statistical Reports of deaths. The occurrence of preventable disease in these weekly lists was checked by direct correspondence with the chief of the medical service in the hospital reporting the death. From him the complete clinical record was obtained. Thereupon a duplicate set of the histologic sections was reviewed and all points of discrepancy reconciled. With this evidence in hand the situation was reconstructed. Then an analysis with criticism and advice was forwarded to the responsible medical chief. Naturally it is impossible to evaluate the profit of such a course of procedure; but there were dividends in improved care of the sick.

The educational program was close to the heart of the Professional Services Division. The routine hospital staff meetings were supplemented by the ETO Medical Society which met periodically in one of the general hospitals. With the growth of the Theater, it was supplanted by regional meetings. Broadening in their influence were the Inter Allied Conferences in War Medicine held in the Royal Society of Medicine under the chairmanship of Sir Henry L. Tidy. The Inter Allied Consultants' Conferences afforded an excellent, but infrequent, medium of interchange. The Operations and Training Division of the Chief Surgeon's Office organized the Army Medical Field Service School at Shrivenham, England, and later at Chateau du Marais, near Etampes, France for the conduct of courses in field medicine and surgery. In a similar vein the 8th Air Force developed the 8th Air Force Provisional Field Service School at High Wycombe, England. With the cessation of hostilities, several ambitious educational programs were initiated by the Training Branch of the Operations Division. Clinical exposures at general practice and specialty levels were evolved in hospital centers. With the coöperation of leaders in internal medicine in Great Britain a splendid preceptorial plan was instituted. Many of the details of these well conceived patterns of training disintegrated with the rapid redeployment in the Summer of 1945.

In 1942 temporary exchanges of medical officers of company grade were arranged between the 5th General Hospital and tactical units in training in North Ireland. The anticipated bilateral advantage was generally acclaimed and warranted its much wider application in the interest of professional advancement and medical care. Apparently unjustified obstacles were placed in the way of its more regular and adequate implementation. For the medical officers of the 8th Air Force periods of observation were arranged in fixed hospitals. Both of these plans gained momentum in the Spring of 1945. In a further endeavor to bring the clinical aspect of the field into sharper focus, a medical follow-up card was prepared. The interested medical officer, transferring a sick soldier from a tactical or detached unit, was merely required to write his own name, unit and APO on

the front of the card and the soldier's name on the reverse side. The first medical officer, giving definitive care to the soldier, would supply the brief salient information as to subsequent course, diagnosis, treatment and disposition. Thereupon by post the card would be returned to the initiating medical officer.

The European phase of World War II was a surgical war. We escaped serious epidemics, and hospital admissions for trauma exceeded those for disease for the first time in military history. Beyond a peradventure, measures of prevention must be given full credit for this amazing record. If a single disease, typhoid fever, notorious as an index of the filth of a campaigning Army, be taken as a guide, we find a most arresting situation (table 1). In four years there were 46 instances of typhoid fever in the

TABLE I

Typhoid Fever

European Theater of Operations, U. S. Army
Cases and rate per 1000 strength per annum, by month and year
February 1942–June 1945 Inclusive

Month	Total	1942	1943	1944	1945
January	4	—	—	3	1
February	1	—	—	—	1
March	6	1	—	—	5
April	3	—	—	—	3
May	3	—	—	—	3
June	8	—	—	—	8
July	—	—	—	—	
August	—	—	—	—	
September	4	—	—	4	
October	—	—	—	—	
November	13	—	—	13	
December	4	—	1	3	
Total	46	1	1	23	21
Rate	.014	.014	.004	.009	.015

Source: Division of Preventive Medicine, Office of the Chief Surgeon, ETOUSA.

American forces in the European Theater of Operations, with two deaths. Living under the variable sanitary conditions of the field, an Army of over three million had a typhoid rate of 0.014 per thousand strength per year, a remarkable tribute to sanitation and typhoid vaccination. The figures for dysentery are somewhat less convincing and they apply only to the period between February 1944 and June 1945, as follows:

	Admissions	Rate/1000
Bacillary dysentery	1,054	0.4
Amebic dysentery	780	0.3
Unclassified dysentery	1,435	0.5

As predicted on many hands the availability of sulfonamides, active in the control of bacillary dysentery, materially reduced the morbidity from this

disease. By the same token the etiologic definition was even less exact than in World War I. Both prophylactically and therapeutically sulfadiazine proved most efficacious. Although there can be little doubt of the occurrence of viral dysentery (Reimann), considerable confusion was interposed by the regular use of sulfonamides in these patients, with or without the benefit of medical advice.

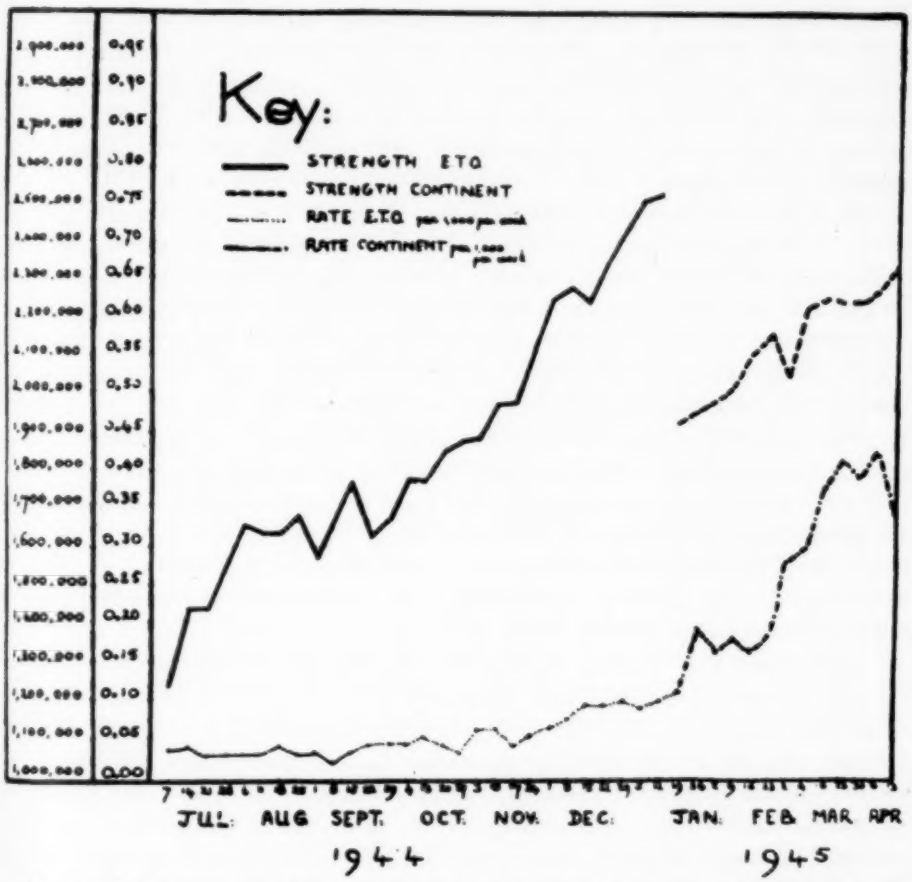

FIG. 2. Infectious hepatitis. The break in the curves of troop strength and disease incidence is necessitated by the availability of records. It will be noted that after the week of January 19, the curves relate to the continent only.

Viral hepatitis constituted a problem of some magnitude in the European Theater. Beginning with the heavy charge of postvaccinial jaundice (yellow fever) in 1942, the naturally occurring hepatitis and homologous serum jaundice were continuously encountered. A total of 22,223 instances was met—an annual rate/1000 strength of 6.99. The curve of incidence (figure 2) found the peak of 952 admissions for hepatitis the week of April 6, 1945. The total number of deaths was 68 (0.3 per cent). In a limited survey of

homologous serum jaundice in this Theater, Kneeland reported 14 deaths among 146 (9.5 per cent). Such experiences multiplied in the several theaters of operations and in the civilian field will unquestionably influence medical thought and practice in the prophylaxis of this preventable type of hepatitis. From a clinical standpoint the remarkable recuperability of the liver was reëstablished; the tests of hepatic function had a limited usefulness; rest and high protein, high carbohydrate, low fat diet with vitamin B_2 supplements were the chief directions of therapeutic attack. A well controlled study in the 121st Station Hospital established no especial advantage of the sulfhydryls over high protein diets. Concurring in the general experience rest was an essential to the most prompt and adequate convalescence. Deferment of rest prolonged the course of viral hepatitis and premature effort usually led to relapses.

Respiratory infections were a lesser source of manpower attrition in Great Britain and Europe than anticipated. In general the curves of incidence were lower in the European Theater than in the Zone of Interior. In the Fall of 1942 primary atypical (viral) pneumonia occurred in great numbers, but it never reached epidemic proportions. Important, however, was its preponderance over bacterial pneumonia through the period of the war (19,477 compared with 12,046). The mortality for primary atypical (virus) pneumonia was 0.2 per cent and for bacterial pneumonia 0.53 per cent. No therapeutic advances were recorded in viral pneumonia. In pneumococcal pneumonia penicillin clearly took priority over the sulfonamides. In November, 1943 virus A influenza made its appearance in an explosive epidemic. It was singularly free from complications and mortality. Had it been the primary wave of a pandemic, the secondary wave would have coincided with the invasion of Normandy!

Meningococcal infections bade fair to be a formidable problem in Europe. Actually there were only 2,138 instances. As compared with the mortality of 38 per cent in World War I, the figure fell from 5.3 per cent in 1942 to 2.8 per cent in 1944. Such improvement arose from early diagnosis and more effective therapy. Sulfadiazine, parenterally and orally, and penicillin, intramuscularly and intrathecally, were stout allies. Antimeningococcus serum was not employed in any degree. Sulfadiazine won its spurs in the chemoprophylaxis of this disease.

From secret sources a high incidence of virulent diphtheria was reported in the Low Countries and Scandinavia before D-Day. On this basis a greatly augmented supply of antitoxin was carried into Europe by our forces. Diphtheria was not an early problem; but soon its occurrence and gravity among German prisoners of war caused concern. At one time in a single camp of 20,000 of these prisoners there was more clinical diphtheria than in the entire United States Army in Europe. Epidemiologists attempted to explain this divergence upon the spacing of immunes in our forces. With increased civilian contacts, however, the disease appeared with increasing

frequency among our troops. In all 1,377 instances were diagnosed; but late complications occurred entirely too frequently. Too much dependence upon the laboratory deferred or obscured the diagnosis. A mortality of 2.3 per cent marred the record.

Typhus fever became a problem after crossing the Rhine. With DDT and the protective vaccination it was never a serious threat to the health of the command. In all, 21 American soldiers suffered from this disease. Where the immune barriers were breached, the disease found expression in a much milder form. None of them died. Malaria appeared largely as a legacy from the Mediterranean area. Most frequently it was the relapsing form of benign tertian malaria. At times clinical manifestations developed for the first time in soldiers parasitized elsewhere. Atabrine discipline was a fluid factor in spite of strong representations and directives. A total of 24,751 victims (or an annual rate/1000 strength of 7.78) was reported. Among these, six (0.02 per cent) died.

From the standpoint of prophylaxis the record for tetanus is unparalleled among the infectious diseases. In the American troops of the European Theater protected by tetanus toxoid followed by a booster dose upon trauma, an isolated instance of tetanus developed. This patient died. Among the German troops only the Luftwaffe and certain paratroop elements received prophylactic vaccination. The remaining unprotected German prisoners of war afforded a horrible control in their high morbidity and mortality from tetanus.

So careful was the screening of inductees that cardiovascular problems were at a minimum. Precocious coronary occlusion arrested passing attention. Rheumatic fever was less frequent than anticipated. Mediastinal trauma gave an unusual opportunity for its electrocardiographic study at the 160th General Hospital. Mass radiography paid fine dividends in the extremely low incidence of tuberculosis in the European Theater. Repeated spot roentgen-ray surveys of selected units by the Senior Consultant in Tuberculosis disclosed no rising incidence of this disease except to a limited degree among nurses over a year in the Theater. The release of RAMPs from Buchenwald and Dachau, among other festering detention camps, suddenly threw an enormous load of far advanced tuberculosis on our mobile and fixed hospitals. Its management in the interest of Allied military and dislocated civilian personnel is a tribute to American Medicine. The Senior Consultant in Tuberculosis organized the work in a most effective manner. The problems in nutrition imposed by the calculated starvation of prisoners by the Nazi were anticipated and met by the combined efforts of the Nutrition Section of the Preventive Medicine Division and experts in the clinical field from the Professional Services Division.

When the Medical Service assumed responsibility for the care of venereal diseases, the Surgeon General left a wise provision. These patients would be treated by the medical officer best qualified to meet their needs. While the

Medical Service could and did care for a majority of the luetic subjects, in many units the urologist continued to treat gonorrhea under the administrative supervision of the Chief of the Medical Service. The experience with the shifting therapy of these conditions differed in no wise from other theaters; but under the Senior Consultant in Dermatology the therapy of syphilis and gonorrhea was consolidated and advanced immeasurably as penicillin became the preferred agent.

The Senior Consultant in Neuropsychiatry marshalled the experience in other armies and in other theaters for the treatment of neuropsychiatric casualties in the European Theater of Operations. Special courses in elementary psychiatry were offered medical officers of tactical units. More advanced courses were given to divisional psychiatrists; but most effective were the lectures for line officers that gave them basic instruction in the recognition and prevention of combat exhaustion. In the field such educational agencies paid fine dividends in limiting losses from these causes.

Reviewing the medical experience of the European Theater of Operations certain salient features emerge. A plan of organization of professional service was evolved on the basis of earlier military experience. Time was afforded to perfect the steps of this organization. The geographic and topographic problems were minimized. The elements were not hostile. Hospitalization to the extent of 140,000 beds was laid on in the United Kingdom before D-Day. Transportation by air, road, rail and sea facilitated movement. The coördination of the several divisions of the Chief Surgeon's Office lent direction and impetus to the purely medical functions emanating from the Professional Services Division. No endemic disease nor serious epidemic was encountered. Superior measures of prevention further limited the incidence of disease. The sulfonamides and penicillin contributed immeasurably to the superb medical record of the Theater; but in the last analysis the largest single factor in the care of our sick was the quality of service that stemmed from the medical training of the past 25 years. Guard well the educational advantage won.

SCRUB TYPHUS IN DUTCH NEW GUINEA *

By Edwin N. Irons and Hiram E. Armstrong, *Chicago, Illinois*

In the course of jungle operations in the islands of the Southwest Pacific, and in the China-Burma-India Theater, Allied forces encountered scrub typhus (Tsutsugamushi disease) in a variety of geographical conditions and with marked variations in the number and severity of cases and speed with which the outbreaks developed. This is a report on 1255 cases of scrub typhus contracted by U. S. Army personnel between June 18 and October 21, 1944 on Owi and Biak islands, off the coast of Dutch New Guinea. All cases were cared for in a 750 bed Army evacuation hospital located on Owi island. Particular interest in this group lies in the large number of cases and the relative mildness of the infection.

Ecology and Epidemiology

The physical features of Owi and Biak islands favorable to the maintenance of the rat-mite-rat cycle of Tsutsugamushi disease have been described by Kohls et al.[1] In contrast to the circumscribed areas of open kunai grass which seemed to be the principal ecological condition associated with scrub typhus in British New Guinea and some neighboring islands, on Owi and Biak islands, abandoned coconut groves, native gardens overgrown with grass and shrubbery, and margins of clearings adjacent to rain forests harbored rats with their parasitic mites. On Biak island, they also seemed to favor corraline ridges covered with low growing trees and native vegetation. Previous outbreaks of scrub typhus among the Allied Forces in the Southwest Pacific Theater had not indicated such areas as actual or potential sources of infection. Because the earlier outbreaks came from infected foci of kunai grass, in later operations this type of area was carefully avoided or cleared and burned over when it became necessary to bivouac or station troops there. However, the epidemic to be described came under new conditions and developed to an extent that was of considerable military importance.

Operations against the enemy commenced early in June; the first cases of scrub typhus appeared in the week June 18 to 24. As personnel poured into the newly occupied areas, the case incidence rose to a peak of 184 cases in the week July 30 to August 5. The first scrub typhus infections in soldiers appeared at about the same time on Biak and Owi islands, but the incidence was less on Biak than on Owi, and the peak of infection on the former was reached about two weeks earlier. Although the area occupied on Owi island was much smaller than that on Biak, a large majority of the cases (891)

* Received for publication September 26, 1946.

appeared on this heavily populated piece of land. A large proportion of the Fifth Air Force personnel (average strength 15,000), was located on Owi island. Seven hundred and sixteen cases of scrub typhus occurred in this group, indicating in a general way the incidence of infection.[2] A larger body of troops on Biak island consisting chiefly of infantry and service units, suffered a lower rate of infection. Many individual units suffered a much

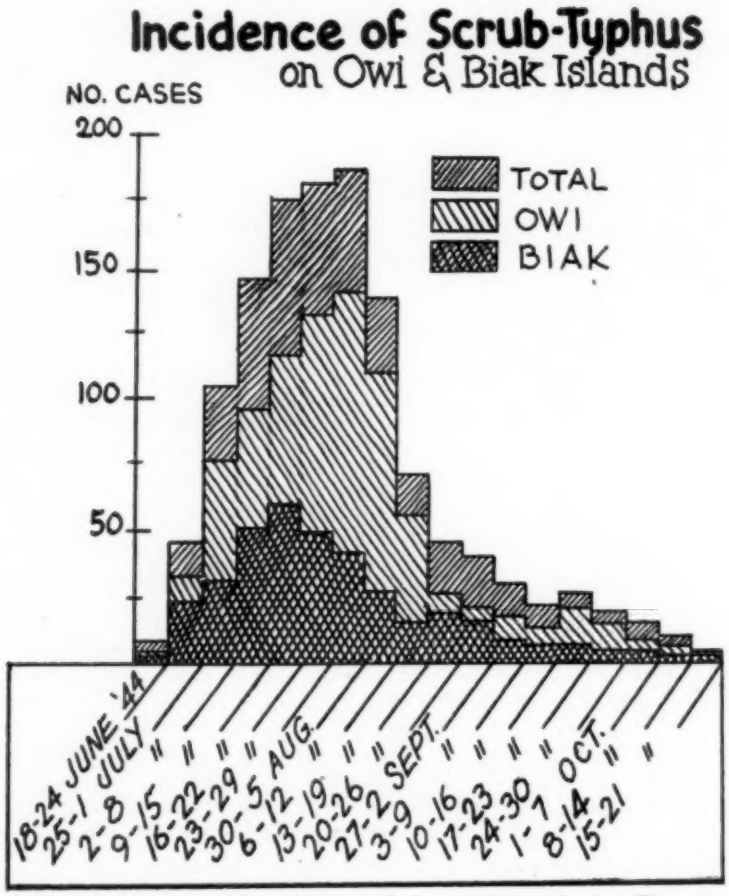

CHART 1. Incidence of scrub typhus on Owi and Biak islands. The case incidence is plotted by weeks and the total number of cases is subdivided into those from Owi and Biak islands.

higher incidence than the general average rate of infection, and in these units the maximum number of cases usually came about three weeks after the first cases were recognized. Within these groups, personnel in positions of leadership were ill in numbers sufficient to decrease these organizations' overall efficiency.

By the end of August, the rapid influx of troops to these new areas was over. The environmental conditions favorable for the maintenance of nat-

ural scrub typhus infection in rats and mites had been recognized and control measures of clearing brush and undergrowth from living areas had been undertaken. Individual protection by impregnation of uniforms with an emulsion of a mite repellant, dimethylphthallate, had also been instituted. These control measures, coupled with a more stabilized situation, diminished the rate of infection to sporadic cases during the middle of October. Chart 1 graphically shows the rapid increase of cases as troops entered infected areas on Owi and Biak islands, and the more gradual decline as environmental and individual control measures were carried out.

Etiology

Rickettsia orientalis (Nagayo et al.), the causative agent of scrub typhus, is transmitted to man by the bite of an infected larval mite, in this case probably *Trombicula Fletcheri,* (Womersley and Heaslip,[1] 1943). The infection is hereditary in mites and is passed to successive generations of the animal reservoir, rats, one of the animals on which the larval form normally feeds. Man serves only as a casual host.

Rickettsiae may be readily isolated from the blood of patients in the febrile stage by intraperitoneal inoculation in white mice. Giemsa-stained smears of the peritoneal exudate of mice so infected show numerous intracellular rickettsiae. This material is infectious for other laboratory animals and the infection may be passed serially in mice by intraperitoneal or other routes of infection.

In this series, eight representative patients infected with scrub typhus were chosen for rickettsial study. All were prostrated with a moderately severe febrile illness varying in duration from two to 16 days at the time blood was withdrawn for mouse inoculation. An eschar was present in four and absent in the others. All showed varying degrees of generalized lymphadenopathy. Five manifested a typical mild erythematous rash during the febrile stage. Six of the eight complained of generalized aches, particularly in the back. One-half of the group had moderate cough, but none developed physical signs of pneumonitis or bronchopneumonia. One showed severe conjunctivitis. There were no severe mental changes, deafness or peripheral neuritis, nor was there jaundice. One patient's course was prolonged by malaria. The total duration of fever varied between nine and 21 days.

All eight groups of mice inoculated intraperitoneally with patients' blood, became infected with *Rickettsia orientalis,* but only four strains were of sufficient virulence to kill the mice so infected. This was in contrast to strains isolated elsewhere whose virulence was almost universally lethal for white mice. The groups of mice surviving were proved to be infected by further surviving challenge doses of 1000 MLD of virulent rickettsiae.[8] There seemed to be little difference clinically between the group of four

patients from whom strains were isolated and passed serially and the other group of four whose bloods produced an inapparent infection in white mice. Two in each group showed eschars, two did not. The days of illness when the bloods were inoculated into mice were roughly parallel in each group, as were the total durations of fever in each. However, all of the group whose bloods produced active transferable infection in mice had sufficient pulmonary involvement to show a cough, while the others did not. This clinical feature might distinguish the severity of infection in the two groups.

The four strains isolated were passed serially by intraperitoneal inoculation in white mice during a five month period. During this time the mice died on an average in 9 to 10 days. Strains of rickettsiae isolated in Papua, New Guinea and from Bat island and observed by us for periods of 15 and seven months were more virulent, killing infected mice on the average in seven and six days respectively. When compared to the Owi-Biak islands strain, this greater virulence was also demonstrated by a 100 to nearly 1000 fold increase in the MLD_{50} titer for white mice. A similar difference in virulence was observed following intraperitoneal inoculation of infectious material in guinea pigs. The Bat island strain caused the highest mortality; the Owi-Biak island strain caused the lowest.

Recently Topping [4] showed cross immunity between strains of rickettsiae, isolated in Papua, New Guinea, Malaya, and from the Assam-Burma border, by inoculating guinea pigs, recovered from a scrub typhus infection, with one of the heterologous strains. Topping found one of the Papuan strains (case 9) least virulent and the Malayan strain the most virulent. He indicated that although cross immunity existed, this did not mean that strains were immunologically identical. Bengtson [5] illustrated this further by showing that serums of man and guinea pigs, recovered from scrub typhus infections, yielded much higher complement fixation titers with the homologous antigens than with antigens made from heterologous strains. She clearly differentiated serologically the Papuan (Karp) strain from the Assam-Burma (Gilliam) strain and indicated that the former was more virulent for white mice. Bell et al.[6] studied the antigenic relationship of three scrub typhus strains by cross neutralization tests. Antiserums produced in rabbits to two strains (Kostival from Papua and Seerangayee from Malaya) neutralized the homologous strain only, but antiserum produced in guinea pigs to Host 21 strains (isolated from mites collected in Papua) partially neutralized heterologous strains.

One of us demonstrated cross immunity between the Owi-Biak strain and a Papuan (Shope) strain by intraocular infections in rabbits.[1] In light of the work of others, this may be interpreted as a general cross immunity between strains of varying virulence, but more detailed study might show serological heterogenicity even in the presence of a common antigenic factor.

Pathology

In this series of 1255 cases there were eight deaths, or a mortality rate of 0.6 per cent. All of these eight patients presented a typical severe scrub typhus course. Six of the group had a well defined eschar and all showed generalized lymphadenopathy. An erythematous rash was observed in seven of the eight patients. All complained of severe headache, and a cough occurred in six of the eight. Of this group with cough, all developed signs of pneumonitis or bronchopneumonia consisting of increased respiratory rates, varying degrees of cyanosis, dullness on percussion of the lung fields, particularly at the lung bases and medium to coarse râles over areas of diminished resonance. During the last days of illness, progressive rise in temperature to 106 to 108° F. occurred with increased pulse and respiratory rates, and fall in blood pressure. Death was probably due to a combination of myocardial and pulmonary insufficiency, and peripheral vascular collapse. The importance of peripheral vascular damage as a factor in fatal rickettsial disease has been emphasized recently by Woodward and Bland in their study of epidemic typhus.[7] Three of the patients manifested striking central nervous system changes characterized by clouded sensorium, delirium, episodes of motor activity and convulsions, signs of meningismus and coma. Here, fatal termination probably resulted in part from this marked central nervous system involvement. Two patients showed severe bleeding tendency, manifested by subcutaneous ecchymoses and hemorrhage in the gastrointestinal tract. Two other patients were jaundiced. The duration of illness before death, one patient excluded, ranged between 13 and 24 days. This excluded patient died on the thirty-second day of illness, with bacillary dysentery. The Weil-Felix reaction in this case rose from no titer on the tenth day of illness to 1 : 5120 on the twenty-sixth day. Histological examination revealed lesions consistent with a healing scrub typhus infection. For these reasons, this was considered a scrub typhus death, although the immediate cause was erosion and bleeding of the large intestine and toxemia (presumably due to bacillary dysentery). *Plasmodium vivax* malaria complicated the course of another patient.

Certain pathological changes, although not striking, characterized the postmortem picture in scrub typhus. The primary eschar, seen at the onset of illness, was present in varying stages of healing at death, but the rash had usually faded. There was frequently a yellow serous effusion, flecked with white exudate, ranging from 50 to 100 c.c. in the pericardial cavity, 200 to 800 c.c. in the pleural cavities and up to 1000 c.c. in the abdominal cavity. The mesenteric, tracheobronchial, retroperitoneal, inguinal, axillary and cervical lymph nodes were frequently enlarged and were grayish pink on cut section. In those patients with clinical signs of pneumonia or pneumonitis, the lungs showed the most marked change. They presented a dark purple mottled appearance, weighed between 500 and 1100 grams and dark

reddish-purple cut sections oozed copious amount of frothy blood fluid. When secondary bronchopneumonia supervened, there were areas of purulent consolidation. The heart showed little gross change, and presented the usual dull beefy red appearance on cut section. Occasionally there were subepicardial petechial hemorrhages. Scattered areas of punctate hemorrhage were also found in the gastrointestinal tract. The spleen was usually enlarged two to four times, and was soft and congested. In those patients showing central nervous signs and symptoms, the brains were slightly edematous with minute hemorrhages in the pons and brain stem, and the meningeal vessels were dilated. Kidneys and testes showed little or no gross change.

The histological picture in scrub typhus, as described by Settle et al.[8] was an acute, generalized endangiitis, vasculitis and perivasculitis which involved most of the organs of the body. Capillaries, arterioles and venules showed endothelial swelling or were thickened by proliferation. The perivascular infiltration was predominantly of plasma cells with some large mononuclear cells and lymphocytes; occasionally, there were polymorphonuclear leukocytes. The interstitial tissues showed varying degrees of edema, hemorrhage and cellular infiltration.

The most marked changes were in the heart which was involved with both a localized and diffuse myocarditis, most prominent in the interventricular septum. Vascular changes were pronounced, there were edema and cellular infiltration of the connective tissue and patchy myocardial degeneration, which varied from cloudy swelling to necrosis of muscle bundles.

The lungs showed interstitial edema and cellular infiltration, with hemorrhage. The alveoli contained edema fluid, occasional leukocytes and red blood cells. In areas of secondary bronchopneumonia, the alveoli and smaller bronchioles showed the characteristic purulent reaction due to bacteria.

In the kidneys were scattered areas of interstitial mononuclear cell infiltration, most frequently seen at the cortico-medullary junction. Some of the glomerular capillaries showed thickening and proliferation; occasionally there was glomerular ischemia, and crescent formation in the glomerular spaces. Areas of tubular epithelium showed cloudy swelling. In the medullary portion of the kidney were small areas of hemorrhage.

The most marked histological brain changes occurred in those patients with neurological signs and symptoms. The meningeal vessels showed a moderate perivascular round cell infiltration, and the small vessels of the brain substance showed a similar reaction in the perivascular sheaths. Infrequently small nodules, described as typical of typhus, occurred in the pons and brain stem and consisted of aggregations of irregularly placed mononuclear cells, glial cells and occasionally polymorphonuclear leukocytes. These nodules were related to small vessels and were associated with edema of the brain substance.

The primary eschar presented coagulation necrosis of the epidermis and superficial corium, and vasculitis and perivasculitis with infiltration of round cells and polymorphonuclear leukocytes. At times there was regeneration of epithelium, although the vascular changes beneath remained.

The spleen and lymph nodes showed an acute splenitis and adenitis, with congestion, edema, hemorrhage and infarction or focal necrosis. Other organs in the body exhibited lesser degrees of vascular change, mononuclear cell infiltration, and occasionally focal hemorrhage.

Variations in Scrub Typhus

Case reports on scrub typhus occurring in New Guinea, India, China, Burma and Malaya [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19] illustrate some of the clinical variations of this disease, and are summarized here. The groups selected were recently reported cases and dealt largely with military personnel. Thus factors influencing the severity of the disease such as youth or old age, sex, race, and intercurrent disease were somewhat reduced and the physical status of the personnel involved was fairly constant. While Lewthwaite's series dealt chiefly with Tamil laborers, of 250 only 20 patients were over 40 years of age. The series reported by Boyd, Machella et al., Tattersall, and Agress et al, included many Orientals. Diseases affecting the course of illness such as malaria, dysentery and parasitic infection were more common among these Asiatic peoples than among the whites.

Reports of earlier case series from regions discussed here and others from Sumatra, Japan, Formosa and its neighboring islands concerned general populations, i.e. male and female, children, vigorous adults, and older people, healthy and debilitated individuals. Among these, the mortality rate was frequently higher and reached 25 to 40 per cent in some instances.

The mortality rates of the groups summarized here, as shown in chart 2, ranged from less than 1 per cent in New Guinea and India to 15 per cent in Malaya. Within some groups there was a considerable variation in mortality. Sangster reported a rate of 3.2 per cent in his first 125 patients from New Guinea, whereas in the next 95 patients, whose disease was contracted farther west in the Ramu Valley, he reported a rate of 14.7 per cent. Similarly, in New Guinea, Williams found a death rate of 1.5 per cent in the first 200 patients with an increase to 25 per cent in the next 150 patients. He attributed this higher rate in part to physical exhaustion of the troops and to a high incidence of malaria and dysentery. Agress, in Assam and North Burma, observed a mortality of 4 per cent in the first group of patients studied with an increase to 18 per cent in the second group. In five groups of patients studied in Assam and Burma by Sayen et al.[20] the mortality varied from none to 16 per cent. Although these patients contracted their disease in various infected foci in Assam and Burma, the writers attributed the differences in mortality to the variation in physical status of the several groups concerned.

Summary of Scrub

Writer	Irons and Armstrong	Boyd	Machella and Forrester	Berry et al.	Mendell	Browning et al.
Location	Owi-Biak Islands	India	China	New Guinea	New Guinea	New Guinea
Year	1944	1935	1943–44	1943–44		1944
No. cases	1255	35	64	195 [85 new cases]	75	173
Mortality	0.6%	Nil	1.6%	[New] 2.4%	2.7%	3.5%
Duration of fever	Ave. 13.7 days [681 cases] 52% 1–13 days 37% 14–20 days 11% 21–30 days	Average: 14.2 days	Average: Chinese 18.3 days American 16 days	Average: 16–17 days	10% 7–10 days 61% 10–20 days 24% 20–30 days	3% <14 days 80% 14–21 days 17% >21 days
Cough, bronchitis and pneumonitis	7.6%		40%		51%	
Broncho-pneumonia and pulmonary complications	1.3%			11.7%		17%
Mental and other central nervous system changes	4.1%	Common	12.5%		48%	
Deafness	0.8%	Nil		33.3%	35%	20%
Peripheral neuritis	0.2%					
Eschar	51%	Nil	67%	80%	68%	80%
Rash	35%	Europ. 71.1% Indians 7.1%	51.5%	Almost all	78%	35%
Adenitis	97%	Nil	93.7%	Usual	95%	
Headache	71%	All	76%			92%
Chill	6.8%		68%			47%
Weil-Felix reaction	Ave. positive 8–10 days [1003 tests]		Ave. positive 14 days	Most: Rising titer or 1 : 160+	Majority 1 : 180+	Most: Rising titer or 1 : 180+

CHART 2. Summary of scrub typhus case reports. data of the several writers and arranged in this

Clinical and rickettsial studies have revealed circumscribed areas which harbored particularly virulent forms of scrub typhus. Such areas have been found in Malaya, on Goodenough island,* and Bat island,** and near Buna and in parts of the Ramu Valley in New Guinea. On the other hand, areas not far removed from these foci of virulent infection harbored a much milder

* On Goodenough island, during a 4.5 month period in October 1943 through January 1944, more than two-thirds of the cases of an epidemic of scrub typhus were contracted in a hospital area. The total cases numbered 69. The mortality, 27.5 per cent, indicated a virulent form of infection.[1]

**South Bat island, in the Purdy group, located 60 miles south of the Admiralty island, was abandoned in April 1944 because of a high incidence of scrub typhus. Among 41 traceable individuals who visited or were stationed on Bat island, there were 26 cases of infection with two fatalities.[21]

Typhus Case Reports

Tattersall	Menon and Ibbotson	Sangster and Kay	Williams et al.	Lipman et al.	Agress and Evans	Lewthwaite and Savoor
India and Burma	N.E. Burma	New Guinea	New Guinea	New Guinea	Assam and Burma	Malaya
1943–44	1944–45	1943–44	1942–44	1943–44	1943–44	1940
500 [200 Europeans]	110	235	626	200	86	250 [15 Europeans]
6% [1000 cases]	8.2%	Ave. 8.5% Oct.–Dec. '43 [125] 3.2% Jan.–Mar. '44 [95] 14.7% Apr.–May '44 [15] 13.2%	Ave. 9.7% 1st 100 cases 1% 2nd 100 cases 2% 3rd 150 cases 25% Last 276 cases 7.2%	10%	Ave. 10% 1st group 55 cases 4% 2nd group 31 cases 18%	15%
Average: 18 days	Average: 15.7 days 23% <10 days Range 5–29 days	Average: 14–21 days Mild 8–10 days	Usual 12–20 days [508 cases] 2% 4–8 days 54% 14–18 days 3% 26–40 days	Ave.: 14–18 days	Average: Gr'p 1—18 days Gr'p 2—21 days	Average: 12–15 days
68%	50%	Common		20%	40%	80%
	6.4%			9%		13%
100%	50%				Mild—almost constant	35%
		15%			28%	Slight 50% Mod. 8% Severe 8% } 66%
2%	5.5%	0.8%		5%		
11%	56%	41%	59%	80%	78%	5%
Europ. 64% Indians 31%	64%	52%	65%	85%	Chinese 31%	Europeans—all Indians—some
92%	98%	Almost universal	66%	98%	94%	40%
100%	100%				86%	92%
					83%	
55% pos. 11 days 80% pos. 15 days 99% pos. 19 days 500 cases 800 tests	Titer of 1 : 125 or over in 82%	Ave. positive 12–16 days Earliest positive 6 days Latest positive 26 days	Titer of 1 : 150 or over in 86%	Positive 9–36 days	Ave. positive 14 days 80% positive 62 patients	Titer of 1 : 125+ or rise in titer in 99%

This summary was prepared from the published chart on the basis of increasing mortality rates.

type. No focus of severe infection was encountered in Dutch New Guinea, although there was a mortality of 3.7 per cent in an epidemic of 931 cases of scrub typhus reported from Sansapor, Dutch New Guinea.[22]

In a comparative rickettsial study in guinea pigs, Topping found the Seerangayee strain from Malaya to be most virulent for these animals. The Gilliam strain, from the Assam-Burma border, was next in virulence for guinea pigs, while the Imphal strain from India was least virulent. The Karp and Case 9 strains from Papua were intermediate in virulence to the Gilliam and Imphal strains. In chick embryos, Bengtson [5] found the Assam-Burma (Gilliam) strain the most and the Indian (Imphal) strain the least virulent. Karp, Seerangayee and Case 9 strains were intermediate in reac-

tion. Rickettsial studies in white mice, performed by one of the authors, showed a Bat island strain to be most virulent and strains from Owi-Biak islands to be least virulent.[8] The Shope strain from Papua was somewhat less virulent than the Bat island strain.

On review of available reports, some of the clinical features of scrub typhus presented by various writers could be correlated with variation in mortality rates and differences in virulence of the causative rickettsial agent for laboratory animals. The average duration of fever ranged from 13.7 days in the less severely ill patients to 21 days in those more severely affected. Cough and the minimal signs of pneumonitis seen in scrub typhus occurred in all the series reported, but the incidence seemed rather variable. Also, secondary bronchopneumonia due to pyogenic organisms and other pulmonary complications occurred with varying frequency. This may be due in part to the manner in which the several authors compiled and presented their data. Although milder cases were separated from the more severe on the basis of locale and mortality, the signs and symptoms of the disease in the different groups were combined. However, detectable pulmonary change was less frequent in our series than in others. Similarly, nervous system involvement characterized by delirium and other mental change, meningismus, eighth nerve deafness and peripheral neuritis was less frequent in our group of patients than in other series in which these changes were discussed. It is significant that many authors commented on the marked severity of illness in those patients with outstanding cardiorespiratory or nervous system involvement.

The appearance of a primary eschar or erythematous rash typical of scrub typhus seemed to have little or no correlation with the severity of illness. One of the determining factors in the development and detection of rash and eschar seemed to be the color of the patient's skin. Rash and eschar were relatively frequent in the white race, whereas they were infrequently reported in the yellow or brown races. However, Anderson and Wing reported 70 per cent eschar and 43 per cent rash in a series of 49 cases of scrub typhus in Melanesians.[23] Regional and generalized lymphadenitis was almost universally present in most series.

The agglutination of Proteus OXK by patients' serums, the Weil-Felix reaction, was a diagnostic aid in most of the series. The reaction became positive on an average between the eighth and tenth days in our series, whereas in others of greater severity and higher mortality, the average positive developed five or more days later.

Clinical Data

The 1255 cases studied in this series were all Army personnel. The great majority were young adults previously in good physical condition. Following the onset of illness, they were hospitalized with reasonable promptness and lengthy evacuation was not necessary as they were all cared for in

the immediate area. Malaria and dysentery were seen in a small proportion of those afflicted with scrub typhus, but these intercurrent infections were of relatively minor importance in the final outcome of the disease in the group as a whole.

The incubation period of scrub typhus in this outbreak appeared to be usually between 9 and 21 days. In many mild cases it was apparently longer but this may well have been due to the fact that the onset of illness was insidious, making it difficult for the patient exactly to date his first symptoms. Indeed, many continued their duties for days after the first mild effects of the disease were felt and some were not hospitalized until an asthenic state, usually seen early in convalescence, developed.

The onset of scrub typhus in the majority of patients was marked by generalized headache (71 per cent) and fever. Mild to moderate prostration was common, and 36 per cent of patients experienced general malaise frequently associated with severe backache. Also, at onset, patients often complained of chilliness, and frank shaking chills occurred in 6.8 per cent.

Fever varied markedly in height and duration. Many of the less severely ill had irregular low grade fever for only a few days. Many other mild cases showed a sustained moderate elevation in temperature for a somewhat longer period. In the more protracted febrile cases, the fever curve rose in a step-like fashion to a maximum varying between 102° and 106° F. The course of pyrexia in these cases closely resembled the typhoid-like fever curves seen in many of the severely ill patients, who contracted the disease in Papua and the Australian Mandated Territory in New Guinea. Temperature returned to normal by lysis of a few days' duration. In a group of 483 patients on whom temperature readings were taken at regular intervals daily, the highest fevers were observed most frequently between the seventh and eleventh days, with the ninth day as an average. The extremes in height of fever ranged between the first and twentieth days. That is, the highest recorded temperature in some patients was seen as early as the first day of illness, whereas in others the maximum temperature occurred as late as the twentieth day. There was also a great range in the total duration of the fever, from one to 30 days. However, the usual duration of pyrexia was eight to 18 days, with an average of 13.7 days. A secondary temperature rise, also noted by some other writers, occurred in 2.2 per cent of the total cases. This rise started two to 10 days after the subsidence of the initial fever, when the patient appeared convalescent, and lasted a few days. It usually occurred in those patients whose original illness was relatively slight, and was accompanied by mild symptoms.

Charts 3 and 4 present graphically the incidence of highest fever in 483 cases and the total duration of fever in 681 cases.

The pulse rate was only moderately elevated during the first week of illness, but during the second and subsequent weeks, particularly in more severely ill patients, pulse rates of 100 to 120 per minute were not infrequent.

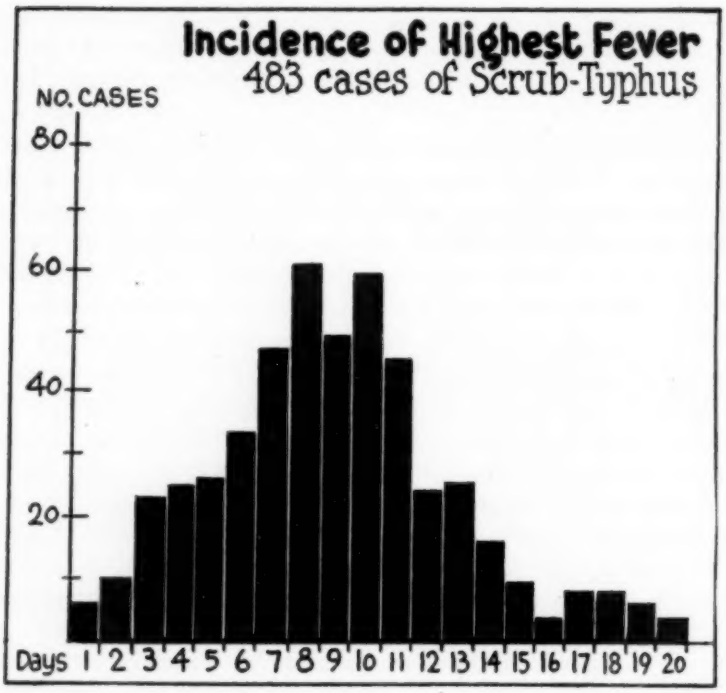

CHART 3. Incidence of highest fever in 483 cases of scrub typhus based on temperature readings taken at four hour intervals.

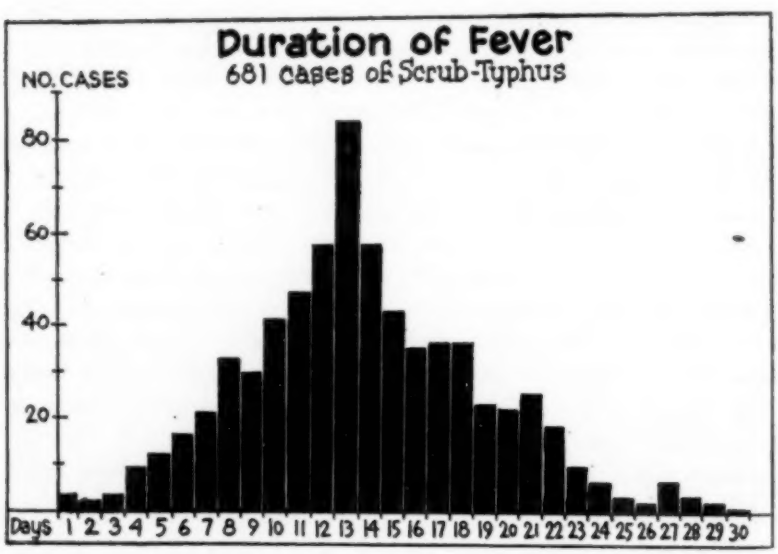

CHART 4. Duration of fever in 681 cases of scrub typhus. Note the maximum incidence on the thirteenth day.

Tachycardia usually subsided with defervescence, but during the early weeks of convalescence it was not uncommon for patients to complain of palpitation associated with a rapid pulse.

A primary eschar, the initial point of rickettsial invasion at the site of attachment of an infected mite, was seen in 51 per cent of patients. Lewthwaite and Savoor first showed immunological identity between rickettsial infections with and without eschar,[18] and repeated clinical and laboratory observations have since confirmed the existence of scrub typhus in the absence of a primary lesion. When present, the eschar was a distinct diagnostic aid. Typically, it measured about a centimeter in diameter, with a raised erythematous border and a black necrotic center. This necrotic area was absent in eschars found in the warm, moist skin folds of the axilla, perineum and other similar locations. In these sites the eschar appeared as a shallow depressed ulcer with well demarcated erythematous border and purulent base. In 23 cases, two or more ulcers were observed simultaneously. As the disease regressed, the necrotic material in the eschar sloughed and epithelium gradually filled the defect. This process was slow and in many cases persisted to early convalescence.

Although mites did not usually crawl from the ground up natural objects such as grass or brush, they were noted to crawl rapidly on foreign objects placed in their natural habitat. An observer on an army cot was reached 1.5 to five minutes after the cot was placed in proximity to mites. On cloth used to make fatigue suits, a group of six mites traveled an average of 11 inches in five minutes.[1] When these mites attacked man, they seemed to have a predilection for the region of pressure between clothing and skin such as the belt line, ankles and beneath leggings. Thus it appeared that the site of the mite attachment was dependent on at least two factors: the availability of a foreign object on which the mites crawled seeking a suitable place, and, secondly, an area of pressure in which they attached.

The distribution of 651 eschars seemed to reflect the natural habits of the mites. Forty-five per cent of all eschars were found on the feet and legs. When soldiers walked or stood in a mite infested area, the legs provided the most accessible location on the body to mites and there were ample pressure areas beneath shoes, leggings and trousers. The folds of skin in the genital, inguinal, axillary, antecubital and popliteal regions formed natural pressure points, and mites seemed to have an affinity for these warm moist areas. Thirty-eight per cent of eschars occurred here although this percentage of mite attachment was much greater than the percentage of body surface represented in these areas. Another general pressure area was at the belt line and seat of trousers. Corresponding to this, 8 per cent of eschars were located on the lower abdomen, iliac crests, lower back and buttocks. The remainder, 9 per cent of eschars, were distributed over the rest of the body. Chart 5 gives a more detailed picture of eschar distribution. Figure 1 shows a typical eschar with black necrotic center located on the buttocks. Figure

2 represents an eschar with a purulent base but without a necrotic center, situated in the antecubital fossa.

Accompanying the primary eschars were varying degrees of adenopathy of those lymph glands which drained the sites of infection. Not infrequently there was associated tenderness, but only rarely was there suppurative change due to secondary pyogenic invasion of these regional glands. Lymph gland enlargement was found in 97 per cent of patients.

Another typical sign was the erythematous rash frequently found in scrub typhus. Between the fourth and eighth days of illness, the dusky

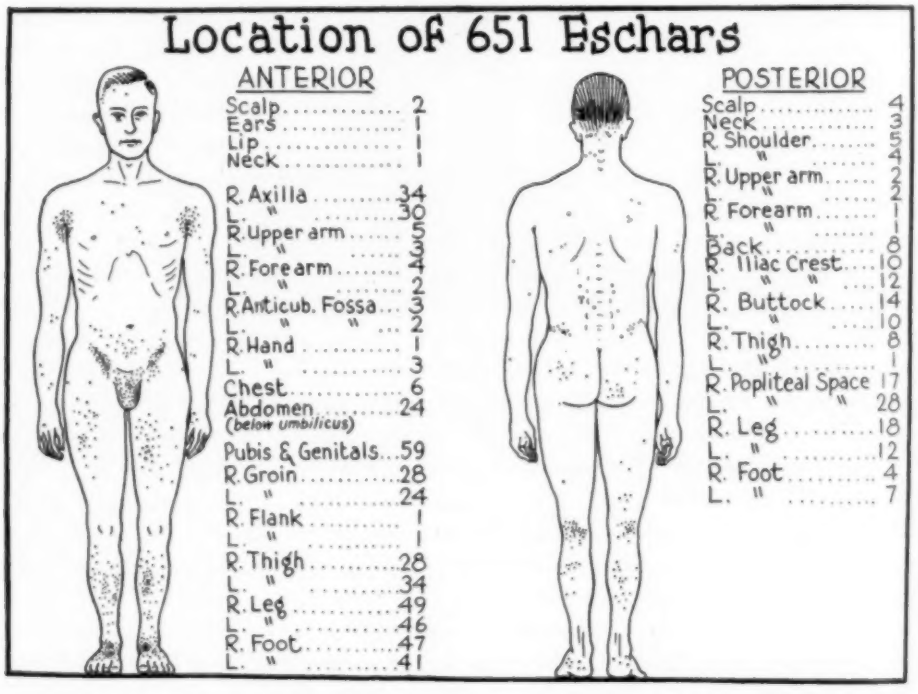

CHART 5. Location of 651 eschars. Note the concentration of eschars in regions of skin folds and pressure points. All eschars found in the axillary, genital and perineal regions are shown on the anterior figure.

red macules appeared characteristically on the trunk and to a lesser degree on the arms and legs. The average time of onset of the rash was 5.6 days after the first symptoms developed. In seven cases, the rash appeared with the onset of the disease, while in 11 cases the rash occurred on the tenth day of illness or later. The maximum time between onset of symptoms and the appearance of a rash was 14 days. The rash usually lasted two to three days, but not infrequently it appeared and faded within 24 hours. Occasionally a slight brown pigmentation remained for a short while after the erythema faded, but a hemorrhagic tendency was not noted immediately con-

nected with the rash. Of the 1255 cases in the group, a rash was found in 439 or 35 per cent.

Cough occurred infrequently in this series, 7.6 per cent of cases, in comparison to its common occurrence in scrub typhus patients seen elsewhere. Pneumonitis, manifested by medium and fine moist râles over the lower lobes, was demonstrated in only a few of the sickest patients. As a reflection of the lowered incidence of marked pulmonary involvement, secondary bronchopneumonia due to pyogenic organisms was seen in only 1.3 per cent of cases.

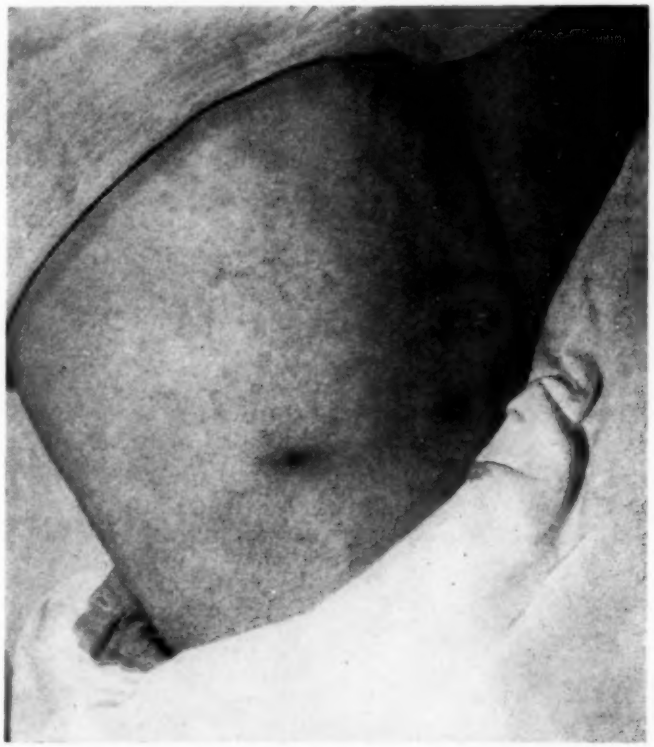

FIG. 1. Eschar on left buttock. Note the black, necrotic center surrounded by a zone of erythema (sixth day of illness).

Similarly, there was a low incidence of severe nervous system involvement. Delirium, confusion, convulsions, and meningismus together occurred in only 4.1 per cent of all cases, although 71 per cent of patients complained of headache. Deafness and peripheral neuritis, not infrequent in the usual cases of severe scrub typhus, appeared in only 0.8 and 0.2 per cent respectively.

The gastrointestinal tract and kidneys were affected clinically in only a small proportion of cases, 6.5 and 1.2 per cent respectively. Nausea and vomiting, and diarrhea followed by constipation, were the usual gastro-

intestinal disturbances. Very rarely was there sufficient bleeding to produce tarry stools. Slight to moderate hematuria, and albuminuria sometimes associated with ankle edema, were the chief signs of kidney involvement. All cleared early in convalescence.

Weil-Felix tests, using a 0.1 per cent formolized culture of Proteus OXK suspended in physiological salt solution, were performed on the serums of patients in all stages of the disease, ranging from the first to the eightieth

FIG. 2. Eschar in right anticubital fossa. Note purulent base and lack of black center (twelfth day of illness).

day of illness. During the first week, 30 per cent of tests were positive, in the second 63 per cent, while in the third the positive tests rose to 87.2 per cent and fell slightly to 82.8 per cent positive in the fourth week. The titers observed ranged from zero to 1:10240. During the first week the lower titers predominated whereas the proportion of high titers was greater in the second and third weeks. Thereafter, the incidence of positive tests and the height of titer in these tests gradually declined, but positive reactions were

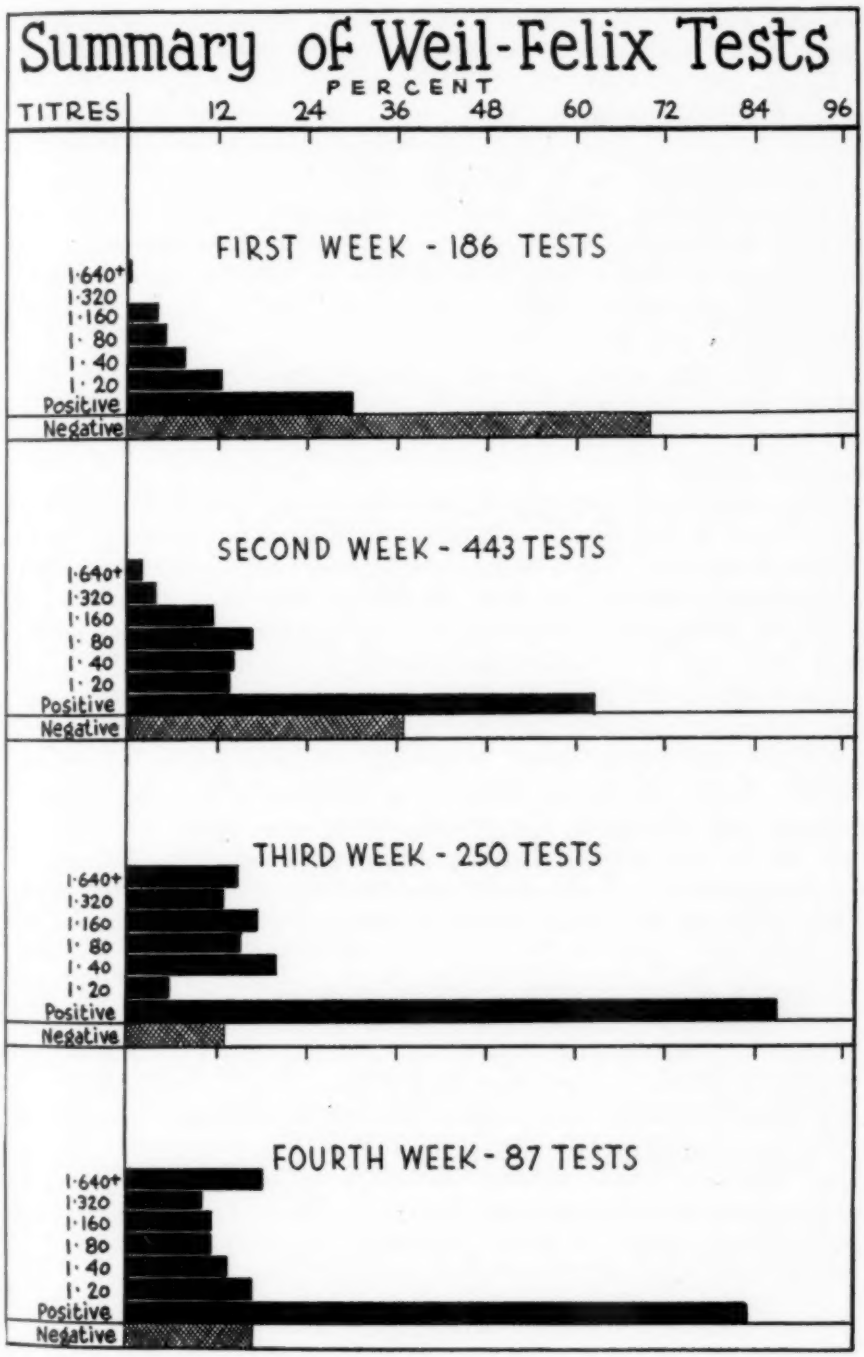

CHART 6. Summary of Weil-Felix tests. The progressive rise in titer is particularly prominent in the second and third weeks.

found two and one-half months after onset of illness. The average initial positive Weil-Felix reaction occurred between the eighth and tenth days of the disease, and reflected again the relative mildness of this particular epidemic. Chart 6 summarizes Weil-Felix tests performed in the first four weeks of illness. A rising OXK titer was observed in over 200 cases, but the remainder of tests represented single observations.

Leukocyte counts ranged between 2,600 and 15,000. Many counts showed a leukopenia with a relative or absolute lymphocytosis. Those patients with secondary bronchopneumonia, or other pyogenic infections, developed a polymorphonuclear leukocytosis. Fall in either hemoglobin or erythrocytes was infrequent.

The urine was usually normal, although sometimes traces of albumin were observed. One case of frank hematuria occurred and small to moderate amounts of albumin were found in the urines of some cases with peripheral edema.

Thirty-nine, or 3.1 per cent of cases showed slight to moderate elevation of the icteric index, which ranged from 10 to 40. Although moderate elevation of the icteric index is occasionally seen in scrub typhus, we thought a concomitant infectious hepatitis complicated the course of at least some patients, as during the same period over 1,000 soldiers from the same commands were under treatment in the hospital for this disease.

Treatment of this group of scrub typhus patients was largely symptomatic. During the febrile period, complete bed rest was the rule. Fluids were forced and supplemented if necessary by intravenous normal saline solution. Extra salt was administered by mouth in many cases. The most appetizing and nourishing diet possible under the circumstances was provided, but the majority of patients lost weight. Sedatives and analgesics were used sparingly. Early in convalescence the mildest cases were returned to their units and the others were evacuated to more fixed hospital installations.

Although we were unable to follow most of the patients during convalescence, a few were readmitted to the hospital two to three months after the initial infection because of asthenia. These patients complained chiefly of weakness, palpitation and easy fatigability. There was little to be observed except weight loss and in some instances a rapid pulse rate. Under a regimen of graded exercise most of these patients improved. None developed signs of cardiac failure. Although not within the realm of this report, it is significant to note that clinicians who studied convalescent scrub typhus patients failed to detect permanent myocardial damage or other persistent late sequelae.[24, 25, 26, 27, 28]

Summary

1. Outbreaks of scrub typhus have been observed under a variety of ecological conditions, sometimes under previously unrecognized circum-

stances; and the disease in different outbreaks has exhibited varying degrees of severity.

2. The degree and extent of natural infections in mites and rodents and the virulence of the infectious agent *Rickettsia orientalis*, in different localities has shown similar variations.

3. Clinical, laboratory and pathological studies are presented, on a group of 1255 patients with typical scrub typhus infection of a relatively mild type.

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THE TREATMENT OF ACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN *

By FREDA WILHELM, M.D., HAROLD L. HIRSH, M.D., HUGH H. HUSSEY, M.D., F.A.C.P., and HARRY F. DOWLING, M.D., F.A.C.P.,
Washington, D.C.

PRIOR to the use of penicillin, the establishment of a diagnosis of acute bacterial endocarditis was tantamount to prophesying the patient's death within one to six weeks. In the literature we have found reference to 40 patients with acute bacterial endocarditis who have been treated with penicillin (table 1).[1-12] Among the 25 patients whose infection was caused by a *Staphylococcus aureus* all but five died. Four of the patients with pneumococcic endocarditis died and two recovered. Five of the seven patients with hemolytic streptococcic endocarditis died, whereas death was reported in the case of one patient with gonococcic endocarditis. Recently a report of a case of meningococcic endocarditis which terminated fatally was published.

We have treated eight patients with acute bacterial endocarditis with penicillin (table 2). Five patients died, the diagnosis being confirmed by necropsy. In the three patients who recovered, the clinical course satisfied the criteria established for the diagnosis of this disease. Since our results appear encouraging we are reporting our experiences in the treatment of these eight patients.

METHOD OF STUDY

Specimens of blood for culture were taken repeatedly from each patient. In every instance two or three positive blood cultures had been obtained before penicillin was started. In two patients, one of whom had been accustomed to taking heroin intravenously, the causative organism was a *Staphylococcus aureus*. A *Staphylococcus albus* was isolated from the blood of five patients. The source of the infection in one of these patients was undoubtedly a chronic pyelonephritis, three were heroin addicts, and in the fifth the source of the infection could not be determined. In the case of the eighth patient, who had pneumonia and meningitis, a type 12 pneumococcus was isolated from the sputum, cerebrospinal fluid and the blood stream.

The sensitivity of two strains of *Staphylococcus albus* was determined before treatment was begun. In each case the initial dosage was the amount estimated as necessary to maintain a constant bactericidal level for each organism, as judged by its sensitivity. These doses were apparently inadequate since the infection persisted and the resistance of each organism to penicillin was found to have increased. The resistance of the hemolytic,

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From the Georgetown and George Washington University Medical Divisions, Gallinger Municipal Hospital, and the Departments of Medicine, Georgetown University School of Medicine and George Washington University School of Medicine.

coagulase-positive *Staphylococcus albus*, obtained from the patient E. R., which had an original sensitivity of 0.39 unit per cubic centimeter increased 16-fold, whereas the resistance of the hemolytic, coagulase-negative *Staphylococcus albus*, obtained from the patient L. M., increased eight-fold, during the time these patients were being treated. The sensitivity of the organisms isolated from the remaining six patients was not determined, and the initial dosage-schedule was established empirically on the basis of past experience with the use of penicillin in the treatment of infections due to similar organisms. The initial dose for all eight patients varied between 5,000 and 30,000 units every two to three hours intramuscularly or 200,000 units per day by continuous intramuscular injection. It was necessary to increase the dose in several of the patients in order to control the infection. The largest dose given was 2,000,000 units daily by continuous intramuscular infusion.

TABLE I

Summary of Reported Cases of Acute Endocarditis Treated with Penicillin

Investigator	Number of Cases	Causative Organism	Duration of Therapy (Days)	Total Doses (Units)	Results	
					Recovered	Died
Case Record No. 29162 Mass. Gen. Hosp.[1]	1	*Staphylococcus aureus*	not given	large doses	0	1
Case Record No. 29371 Mass. Gen. Hosp.[2]	1	*Staphylococcus aureus*	10 hours	200,000	0	1
Keefer et al.[3]	9	*Staphylococcus aureus*	4 to 52	270,000 to 2,340,000	0	9
Herrell[4]	2	*Staphylococcus aureus*	not given	not given	0	2
Dawson and Hobby[5]	1	*Staphylococcus aureus*	3	480,000	0	1
Harford et al.[6]	2	*Staphylococcus aureus*	6 to 13	270,000 to 3,157,000	0	2
Meads et al.[7]	1	*Staphylococcus aureus*	16	3,820,000	0	1
Dolphin and Cruickshank[8]	3	*Staphylococcus aureus*	12 to 24	646,000 to 2,044,000	2	1
Anderson[9]	1	*Staphylococcus aureus*	5	1,000,000	0	1
Glaser et al.[10]	4	*Staphylococcus aureus*	6 to 35	270,000 to 2,340,000	3	1

TABLE I—*Continued*

Investigator	Number of Cases	Causative Organism	Duration of Therapy (Days)	Total Doses (Units)	Results	
					Recovered	Died
Present series	2	*Staphylococcus aureus*	1/8 to 56	25,000 to 13,440,000	1	1
Present series	5	*Staphylococcus albus*	1 to 107	865,000 to 81,120,000	2	3
Meads et al.[7]	2	Hemolytic streptococcus	1/4 to 14	30,000 to 445,000	1	1
Dolphin and Cruickshank [8]	3	Hemolytic streptococcus	10 to 15	960,000 to 2,300,000	3*	0
Anderson [9]	1	Hemolytic streptococcus	8	960,000	0	1
Cataldo [11]	1	Hemolytic streptococcus	11	1,420,000	1	0
Dawson and Hobby [6]	3	Pneumococcus	3 to 7½	172,500 to 384,000	0	3
Meads et al.[7]	3	Pneumococcus	6 to 18	975,000 to 3,285,000	2	1
Present series	1	Pneumococcus	27	1,040,000	0	1
Meads et al.[7]	1	Gonococcus	3	330,000	0	1
Firestone [12]	1	Meningococcus	not given	not given	0	1

* One patient died later with evidence of healed endocarditis.

Since others,[13] as well as two of us,[14] have not encountered relapses in patients with subacute bacterial endocarditis treated with penicillin for eight consecutive weeks, it was decided to treat all patients with acute endocarditis for this same length of time.

RESULTS

Patients who are adequately treated with penicillin may die of overwhelming infection, congestive heart failure or embolic phenomena. Three of our patients, E. R., W. W. and J. M., all of whom were treated for two days or less, died as a result of the infection itself. A fourth patient, O. B., received inadequate dosages. At the time this patient was under treatment the supply of penicillin was scarce and she received 5,000 to 10,000 units every two to three hours intramuscularly. One patient, F. B., with aortic

TABLE II

Results of Penicillin Therapy in Eight Patients with Acute Endocarditis

Patient	Age	Sex	Color	Source of Infection	Duration of Infection (Days)	Causative Organism	Hemolysis	Coagulase	Valves Involved	Other Diseases	Complications Which Developed During Treatment	Duration of Treatment (Days)	Results	Follow-up
W. W.	13	M	W	Unknown	8	*Staphylococcus aureus*	Positive		Mitral	Rheumatic heart disease	Embolism of left popliteal and dorsalis pedis arteries	1/8	Died	Autopsy
J. F.	35	M	N	Heroin Addict	7	*Staphylococcus aureus*	Negative		Tricuspid	Toxic nephritis Skin abscesses	Pulmonary infarction	56	Recovered	20 months
E. R.	36	M	N	Unknown	8	*Staphylococcus albus*	Positive	Positive	Mitral Aortic	Rheumatic heart disease	Cerebral and splenic infarction	1	Died	Autopsy
J. M.	62	M	N	Pyelonephritis	56	*Staphylococcus albus*	Positive		Mitral	Arteriosclerosis	Renal and splenic infarction	2	Died	Autopsy
O. B.	25	F	N	Heroin Addict	21	*Staphylococcus albus*	Negative	Positive	Tricuspid	Pregnancy Exfoliative dermatitis	Multiple septic infarctions	8	Died	Autopsy
A. S.	38	M	N	Heroin Addict	21	*Staphylococcus albus*	Negative		Tricuspid	Malaria	Pulmonary infarction	56	Recovered	20 months
L. M.	38	F	N	Heroin Addict	14	*Staphylococcus albus*	Positive	Negative	Tricuspid	Malaria	Pulmonary infarction	107	Recovered	7 months
F. B.	43	M	N	Pneumonia	40	Pneumococcus, Type 12			Aortic	Meningitis	Congestive heart failure	27	Died	Autopsy

valve involvement, died suddenly as the result of acute left ventricular failure following severe exertion at a time when the infection had apparently been brought under control by penicillin. The three patients who recovered were treated continuously for at least 56 days.

Although embolic episodes occurred in all but one of our patients, no deaths could be attributed directly to these complications. Four patients had clinical and roentgenological evidences of pulmonary infarction, and all of these had involvement of the tricuspid valve. Splenic infarcts were observed in three patients, renal infarcts in two and occlusion of the left popliteal and dorsalis pedis arteries in one.

Acute bacterial endocarditis may affect hearts previously undamaged but it occurs more frequently in those already affected with rheumatic or congenital lesions. There was evidence of a preëxisting heart lesion in two of our patients. In patient W.W. there was a history of rheumatic fever three years prior to admission, and at necropsy there was evidence of rheumatic mitral valvulitis. In patient E. R. there was no history of rheumatic fever but rheumatic disease of the mitral valve was present at autopsy.

An analysis of data concerning the valves affected revealed that one patient had involvement of the aortic valve, two of the mitral valve, and another of both of these valves. The valve most commonly involved in this group of patients was the tricuspid, this being the site of the infection in five patients.

Other diseases were present in seven of the eight patients. The one disease which offered the most difficulty in differential diagnosis initially, and as a possible cause of fever during therapy, was malaria. This infection has been found frequently in heroin addicts in this hospital, and as has been mentioned before, five of our patients were heroin addicts. Two of the patients developed fever and chills during treatment, and it was thought that the endocarditis had relapsed. However, repeated blood cultures on media containing penicillinase showed no growth, and eventually malaria parasites were found in blood smears. Both patients recovered after atabrine therapy.

Summaries of the histories of the three patients who have recovered are presented.

Case Reports

J. F., a 35 year old Negro male, was admitted with the complaint of daily chills for the preceding week. Except for the fact that he was a heroin addict the history was irrelevant. Physical examination revealed multiple abscesses of both upper extremities, a generalized erythematous rash and numerous petechiae. Although the initial examination of the heart revealed no abnormality, within several days a blowing systolic murmur was heard over the tricuspid area. This murmur persisted throughout the hospital course, but decreased in intensity as the patient improved. There were physical findings of consolidation over the right lung, and roentgenological examination was suggestive of pulmonary infarction. These findings disappeared after two weeks. In the interim, six blood cultures were reported positive for a *Staphylococcus aureus*. He was started on 200,000 units of penicillin by continuous intramuscular

infusion daily. After a few days, intermittent intramuscular injections of 20,000 units at two-hour intervals were substituted. He made an uneventful recovery after 56 days of treatment and was discharged after 108 days in the hospital.

One year later this patient returned with a history of pain in the left side of the chest and hemoptysis. In the meantime he had resumed the use of heroin. On admission there were signs of consolidation over the left lower lobe. A very faint systolic murmur was heard over the tricuspid area. This murmur was hardly audible and no change was noted during this hospital stay. The diagnosis was lobar pneumonia and he was placed on a regime consisting of 75,000 units of penicillin every three hours by mouth. There was no improvement after 72 hours of treatment and in the meantime a *Staphylococcus aureus* was twice grown from the blood. He was then given 500,000 units of penicillin per day by continuous intramuscular infusion. When the blood cultures remained positive and the resistance of the organism was found to have increased eight-fold the dose was increased to 1,000,000 units per day. In spite of these high doses the infection remained uncontrolled, and penicillin was discontinued after 10 days. Sulfadiazine was then given for four days without response. The organism was found to be sensitive to 0.22 unit per cubic centimeter of streptomycin and he was started on a course of 5,000 units every four hours by intermittent intramuscular injections. The fever subsided within two days and the course thereafter was uneventful. Streptomycin was administered continuously for 56 days.

Comment. This patient was of particular interest because he was apparently cured of acute endocarditis on his first admission, and returned one year later with clinical symptoms of bacteremia. He had in the meantime resumed the use of heroin by intravenous injection. The staphylococcus recovered on the second admission was different from the organism causing the previous infection, and therefore it is certain that this illness represented a reinfection rather than a recurrence. A definite diagnosis of acute endocarditis could not be made at this time because no change in the tricuspid murmur occurred and no new murmurs were heard. The high resistance to penicillin and low resistance to streptomycin of the organism causing the second infection was also of interest. While the patient continued to show signs of overwhelming infection during the administration of large doses of penicillin he made a remarkable clinical improvement within the first 24 hours after streptomycin was started.

L. M., a 38 year old Negro woman, was admitted with a history of cough, pain in the left side of the chest and chills. She was a heroin addict, although she denied having taken the drug for eight months prior to admission. Physical examination revealed evidence of consolidation over the left lower lobe. It was thought that the patient had pneumonia, and she was given 15,000 units of penicillin every three hours intramuscularly. On the second hospital day she developed bilateral thrombophlebitis in the lower extremities, and roentgenological evidence of pulmonary infarction. Both femoral veins were ligated.

The high incidence of bacteremia which has been observed in heroin addicts in this hospital [16] prompted us to take daily blood cultures. Three of these were positive for a *Staphylococcus albus*. On the ninth hospital day a blowing systolic murmur was heard over the tricuspid area. This murmur increased in intensity and persisted throughout the period of observation. At this time it was thought that the patient had acute endocarditis of the tricuspid valve. The initial dose of penicillin was not changed during the first three weeks of treatment because the patient showed clinical

improvement and the blood cultures remained sterile. On the twenty-second hospital day the patient developed fever, and the *Staphylococcus albus* was again cultured from the blood. The dose was increased to 50,000 units every two hours, since the resistance of the organism had increased four-fold. When the patient improved it was decided to maintain this dose. After one month on this regimen the patient again had an exacerbation of symptoms and the organism was again found on blood culture. The dose of penicillin was therefore increased to 2,000,000 units per day by continuous intramuscular infusion. A few days later this dose was reduced to 1,000,000 units when it was found that the resistance of the organism had increased only two-fold. The course thereafter included a bout of malaria which was treated successfully with atabrine. Treatment with penicillin was continued for 56 days following the last exacerbation.

Comment. This patient aroused much interest while under observation. Although she was a heroin addict, she denied the use of the drug intravenously for eight months prior to admission. This kind of history is usually unreliable, however, and it seems unlikely that an infection related to the use of heroin would have remained latent for eight months. On admission the question of whether the patient had pneumonia or pulmonary infarction arose, and from the subsequent course it was thought she had the latter. During each exacerbation she responded symptomatically to what proved to be inadequate doses of penicillin, and during each of these periods the resistance of the organism increased. Ultimately the dose of penicillin was increased sufficiently to control the infection.

A. S., a 38 year old Negro male, was admitted to the surgical ward with a history of having been ill for three weeks with chills, fever and pains in the chest and both thighs. Four days prior to admission he had developed abdominal pain. The remainder of the history, as given, was irrelevant. Physical examination revealed a temperature of 103° F. and pulse of 110. No abnormalities of the heart were found. Crepitant râles were heard over the base of the right lung posteriorly, direct and rebound abdominal tenderness was present over the right upper and lower quadrants, and there was exquisite tenderness of both thighs, more marked on the left. Although the patient had numerous scars over the veins of both forearms, on admission he denied the use of opiates by injection. Later, however, the patient admitted the use of heroin by intravenous injection. Roentgenological examinations of the chest, abdomen and thighs revealed no abnormalities. A tentative diagnosis of ruptured appendix with subdiaphragmatic abscess was made, and symptomatic and supportive measures were instituted.

There was no change in the patient's condition during the first 48 hours. At this time the patient was started on penicillin therapy, 20,000 units every three hours intramuscularly plus sulfadiazine by mouth, in doses of one gram every four hours following an initial dose of four grams. When this therapy had been continued for several days and no improvement had been noted, the sulfadiazine therapy was discontinued. The patient was then transferred to the medical service for further study. At this time treatment with penicillin was stopped also.

Another roentgen-ray examination of the chest revealed findings suggestive of pulmonary infarction. By the ninth hospital day a *Staphylococcus albus* had been cultured from two specimens of blood. At this time penicillin was resumed in doses of 20,000 units every two hours intramuscularly. The patient continued to have daily fever, however, and several days later the dose of penicillin was increased to 30,000 units every two hours. The remittent fever continued; nevertheless. The signs of

persistent infection and the experience of having found malaria previously in heroin addicts prompted us to look for malaria parasites. Blood smears were found to contain plasmodia, while repeated blood cultures with media containing penicillinase were sterile. The patient was then given a course of atabrine with prompt decline of the fever, following which the dose of penicillin was reduced to 20,000 units every two hours. During the third week and for the remainder of his hospital stay a harsh systolic murmur was heard over the tricuspid valve area. It was at this time that the diagnosis of acute tricuspid endocarditis was made. Penicillin was continued for 56 days.

Comment. This patient was of interest for several reasons. The bizarre symptoms and signs on admission obscured the diagnosis at first. The presence of malaria further confused the picture. Ultimately the diagnosis of acute endocarditis was established on the basis of the following facts: a history of the use of heroin by injection with unsterile instruments, positive blood cultures for a *Staphylococcus albus,* evidences of pulmonary infarction and the development of a persistent murmur over the tricuspid valve area. This patient demonstrates two of the complications of heroin addiction commonly seen in this hospital, acute endocarditis and malaria.

Discussion

Penicillin has materially altered the prognosis in acute endocarditis. Whereas formerly all patients with this disease died, an increasing number of reports of cases cured with penicillin are now being published. It has been stated that acute staphylococcic endocarditis results in the highest mortality, whereas in streptococcic and pneumococcic infections the prognosis is somewhat better.[9] We are unable to confirm this observation because all the infections in our patients with the exception of one were caused by the staphylococcus. Moreover, the three patients in our series who recovered had staphylococcic infections.

Analysis of the results of treatment in our series of patients fails to show any relationship between the duration of the infection before treatment was started and prognosis. It will be seen from table 2 that symptoms of the disease had been present for one to three weeks prior to admission in the three heroin addicts who recovered, whereas other patients who had been ill for only eight days died. In itself this observation suggests that these heroin addicts were able to combat the infection more effectively. Undoubtedly they inject some bacteria along with the heroin with the use of unsterile instruments, and consequently develop increasing resistance to infection. Furthermore, blood cultures were taken on all the heroin addicts on admission to the hospital, whereas they were not obtained on the other patients until the symptoms suggested the diagnosis of bacteremia or endocarditis. This practice led to the establishment of the diagnosis and institution of therapy before the disease became uncontrollable in the heroin addicts.

One has only to witness the fulminating course of a patient with acute endocarditis to be convinced that the only hope in this disease lies in early

diagnosis and vigorous treatment. Although the mortality in this group of cases is lower than in previously reported series, it is still extremely high. Analysis of the cases reveals that of the five patients who died, four probably were inadequately treated. The diagnosis was established late in the course of the disease in three of these patients so that penicillin had been administered for two days or less before death. In one patient there was such extensive involvement of the aortic and mitral valves that although he was treated for only one day, it is hard to believe that any amount of penicillin would have been of avail.

Whenever possible, the sensitivity of the causative organism should be determined and the dose of penicillin established accordingly. If the sensitivity of the organism to penicillin has not been determined, doses of 500,000 units per day should be given, since most cases of acute endocarditis are caused by staphylococci. These organisms are usually relatively resistant initially, or may easily develop resistance to penicillin, particularly when concentrations of the drug are inadequate.

The left side of the heart is predominantly involved in acute endocarditis. Staphylococci, streptococci and meningococci involve the mitral valve more frequently, whereas pneumococci and gonococci involve the aortic valve more commonly. When the right side of the heart is affected, it is usually at the tricuspid valve. The aortic and mitral valves were involved alone or in combination in four of the patients in this series. Pneumonia and pyelonephritis were the sources of infection in one each of two of these patients, and the source was undetermined in the other two. Since tricuspid endocarditis was found only in the four heroin addicts it is thought that this observation may be explained by the fact that the organisms were introduced directly into the veins and reached this valve first and in great numbers. There is apparently no significance to the observation that the three of the four patients with tricuspid valve involvement recovered, while the patients with lesions on the other valves died.

Although seven of the eight patients had evidence of embolic phenomena, only those patients with involvement of the tricuspid valve had pulmonary infarction. This is obviously explained by the anatomical relationship between this valve and the lungs. There were no deaths attributable to this complication.

Summary and Conclusions

1. Eight patients with acute endocarditis were treated with penicillin. Three with staphylococcic endocarditis recovered while four patients with staphylococcic and one with pneumococcic endocarditis died.

2. In the presence of symptoms of infection, the diagnosis of acute endocarditis should be entertained and repeated blood cultures taken. The usual acute fulminating course of this disease makes it mandatory that penicillin therapy be instituted early if success is to be achieved.

We wish to thank the members of the Georgetown and George Washington Medical Divisions, Gallinger Municipal Hospital, for their kind coöperation in the management of these patients, and Miss C. Barbara O'Neil for technical assistance.

Since this paper was submitted for publication two patients known to be heroin addicts with acute endocarditis have been treated successfully with penicillin.

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CARDIAC ARRHYTHMIAS COMPLICATING TOTAL PNEUMONECTOMY *

By Edward Massie, M.D., F.A.C.P., and Anibal Roberto Valle, M.D.†
St. Louis, Missouri

The surgical removal of the entire lung is the only method of treatment which has been employed to date that has been at all efficacious for pulmonary carcinoma. Many special problems attend removal of such a vital organ. Chief among the difficulties encountered is the effect on the heart and remaining lung of the abrupt shunting of the entire pulmonary circulation through the vascular bed of the one undisturbed lung. This fact takes on even more importance when one considers that there is probably no other part of the body, the derangements of which have such a profound influence upon the well being of man as those of the cardiovascular system. In addition it is important to point out that a disturbance of circulatory function suddenly developing will give rise to much more profound symptomatic effect than will one that develops insidiously over a prolonged period. In pneumonectomy, the disturbance is certainly precipitous.

The development of intrathoracic surgery was not accelerated until information accumulated regarding the various physiological factors that interfere with respiration and circulation when the chest is widely opened by the surgeon, and appropriate countermeasures became available to prevent or minimize these disturbances during and after operation. Once this was accomplished, other anatomic and technical details were developed for the operation of total pulmonary resection. One aspect, however, that has escaped sufficient attention until recently is the comparatively high incidence of dangerous cardiac arrhythmias following pneumonectomy and the resultant increased morbidity and mortality from the deteriorating effect of the arrhythmias upon the functional state of the heart. There is already abundant experimental and clinical evidence to indicate a profound immediate change in the electrocardiogram as a result of such procedures as pulmonary vessel ligature and lung collapse just prior to pneumonectomy. In animals, twisting of the lung hilus or incomplete clamping of the pulmonary artery has been shown to cause a negative effect upon the T-wave.[1] Krumbhaar [2] noted, following pulmonary artery ligature an increased amplitude of the P waves and frequent extreme ventricular deflections. Another group of workers [3] encountered five instances of transient cardiac arrhythmias in addition to T-wave changes following pneumonectomy in 11 dogs. In the past year, several clinical articles [4, 5] have appeared calling attention

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From the Departments of Medicine and Surgery, Washington University School of Medicine, and the Chest Service and Heart Station, Barnes Hospital, St. Louis, Missouri.
† Fellow in Chest Surgery from Buenos Aires, Argentina.

to the occurrence of abnormal cardiac rhythms following thoracic surgery in humans. The present study was undertaken in order to determine the frequency with which cardiac arrhythmias have been encountered at Barnes Hospital following pneumonectomy and to attempt to discover the cause or precipitating factors that help initiate these arrhythmias.

Results

In an analysis of a series of 120 patients undergoing total lung resection, 11 or 9.1 per cent were found to have developed a detectable arrhythmia sufficient to have endangered the outcome of the operation or at least to have caused symptomatic difficulty. The operations were performed by Drs. Evarts A. Graham, Brian Blades, and J. Karl Poppe. The arrhythmias

Table I

Incidence of Arrhythmias in Relation to Type of Pulmonary Lesion

Lesion	No. of Cases	No. of Arrhythmias	Per Cent
Bronchiogenic carcinoma	70	8	11.4
Mixed tumor	20	1	5.0
Bronchiectasis	11	2	18.2
Cystic disease	10	—	0.
Lung abscess	5	—	0.
Stricture of bronchus	2	—	0.
Fibrosarcoma	1	—	0.
Actinomycosis	1	—	0.
Total	120	11	9.1

included five instances of auricular fibrillation, four of auricular flutter and one each of frequent auricular and ventricular extrasystoles. As shown in table 1, the operations were performed for various types of pulmonary disease, the predominant one being bronchiogenic carcinoma. The right lung was removed in six of the patients developing postoperative arrhythmias and the left in five. Table 2 shows the location of the lesion with reference to

Table II

Incidence of Arrhythmias in Relation to Location of Pulmonary Lesion

Lobe or Bronchus Involved	No. of Cases					
	Right Lung	No. of Arrhythmias	Per Cent	Left Lung	No. of Arrhythmias	Per Cent
Upper	20	2	10.	17	3	17.6
Lower	17	1	5.9	16	1	6.3
Middle	2	0	0.	—	—	—
Lower and Middle	3	2	66.6	—	—	—
Main	18	1	5.5	27	1	3.7
Total	60	6	10.	60	5	8.3

the lobes or bronchi involved. The type or location of the lesion had no specific relation to the occurrence of the arrhythmias, although abnormal cardiac rhythms did develop in two of the three patients with involvement of more than one lobe. Analysis of the presenting symptoms of the patients revealed the usual complaints of cough frequently associated with sputum, dyspnea, hemoptysis, weight loss, pain, fever, and weakness but no correlation could be detected between these symptoms and the subsequent development of cardiac disturbances.

All the patients developing arrhythmias were 35 years of age or older, the greatest incidence being between the ages of 40 and 70 years. Forty-two of the patients having a total pneumonectomy were under 35 years of age and actually 15 of these were children. Although of the total of 120 cases, 9.1 per cent developed abnormal cardiac rhythms, if we exclude the younger patients under 35 years from the group, the incidence percentage rises to 14.3 per cent. This difference is to be expected since the hearts of young

TABLE III

Incidence of Arrhythmias in Relation to Age

Ages	No. of Cases	No. of Arrhythmias	Per Cent
1 to 10	11	—	0.
10 to 20	7	—	0.
20 to 30	16	—	0.
30 to 40	9	1	11.1
40 to 50	32	4	12.5
50 to 60	36	4	11.1
60 to 70	9	2	22.2
Total	120	11	9.1

people are generally in comparatively good condition and not prone to the development of cardiac accidents. Table 3 shows the number of cases and arrhythmia-occurrences in each age group.

In the total of 120 cases, mass ligation of the hilar structures was used in 29 patients with the development of cardiac arrhythmias in two instances (6.9 per cent), whereas the preferable individual ligation technic was used in the remaining 91 patients with nine abnormal rhythms developing (9.9 per cent). This difference hardly appears significant in this small group of cases. Of the patients developing arrhythmias postoperatively, eight were males and three females. From this sex difference, however, it is not to be concluded that these occurrences are more prevalent in men because three times as many males were operated upon as females. Study of the extent of the anemia before and after operation and the number of transfusions given the individual patients revealed that these factors had no influence upon the development of the cardiac abnormalities. Similarly no correlation was detected between febrile reactions and the cardiac disturbances encountered in

this study. Medications given prior to the development of the cardiac difficulties also presented no etiologic clue.

All the arrhythmias developed within one week after operation, one instance occurring on the second postoperative day, six on the third, two on the fourth, and one each on the sixth and seventh postoperative days. These time elements would indicate that the first seven days after operation are the ones which should be most carefully observed for the appearance of abnormal cardiac rhythms. The occurrence of arrhythmias apparently bore no relation to the development of other postoperative complications for whereas only four of the 11 patients with heart disturbances developed postoperative empyema and bronchial fistulae, slightly less than half of the others manifested these complications. Three of the patients with cardiac arrhythmias died and an extensive pericarditis was found in the two subjected to postmortem examination. Occurrences of unusually rapid mediastinal shift appeared to bear no relationship to the incidence of abnormal cardiac rhythms. Since a previous report [4] suggested that vagal irritation from bronchial stump infection may precipitate the arrhythmias and since vagal stimulation has been shown to induce auricular fibrillation under certain conditions, consideration was given to the correlation of possible excessive vagus nerve manipulation or disturbance during or after operation with the occurrence of arrhythmias but no relationship could be discerned.

Twenty-six of the total group of 120 patients presented some evidence of heart involvement prior to operation either on physical or more frequently on electrocardiographic examination. Two of these patients actually had a diagnosis of right bundle branch block on their preoperative electrocardiograms. It is interesting to point out that only in one of these 26 cases was a detectable postoperative arrhythmia encountered whereas the remainder of the arrhythmias appeared in patients with presumably adequately functioning hearts preoperatively. Further study revealed that in addition to the 11 patients developing abnormal cardiac rhythms and symptoms therefrom, at least six other individuals showed some objective physical or electrocardiographic evidence of cardiac difficulty not present preoperatively. In this connection it is important to point out that total removal of a lung did not result in a single instance in the appearance of a coronary pattern in the electrocardiogram postoperatively. Careful study of this subject was stimulated by the fact that one of the patients, nine months following his pneumonectomy, developed a typical attack of coronary thrombosis associated with the usual electrocardiographic changes. After reviewing 31 cases in which electrocardiograms were available before and after operation, and following a special study of an additional 15 patients in which not only the routine but also fourth leads had been obtained before operation and upon discharge from the hospital, no instance was encountered of the development of a coronary pattern in the electrocardiogram as a result of the total lung removal. Furthermore, since so many of these patients are in the age group

where coronary accidents are prone to occur, such complications are to be expected without necessarily being connected with the previous operation of total lung resection.

Case Reports of Nine Patients With Postoperative Auricular Fibrillation or Auricular Flutter

Case 1. L. D., a 63 year old white woman, had had a productive cough for the past eight years and fever for one year. Physical examination showed massive atelectasis of the right lung; bronchogram and bronchoscopy revealed a block of the right main stem bronchus. A diagnosis of mixed tumor of the right main bronchus was made and the patient had a total pneumonectomy with mass ligation of the hilar structures. Auricular fibrillation developed on the third postoperative day and in spite of digitalis treatment for five consecutive days, the patient died on the eighth postoperative day.

Case 2. M. W., a 48 year old woman, had had a productive cough for six months and weakness for three months. On physical examination she was found to have a massive atelectasis of the right lung. Bronchogram together with bronchoscopy revealed a block of the right main stem bronchus. A diagnosis of bronchiogenic carcinoma of the right main bronchus was made, and a total pneumonectomy was performed by individual ligation technic. Except for the development of auricular flutter on the fourth postoperative day the patient made an uneventful recovery. The arrhythmia disappeared without specific medication and the patient was discharged in good condition. When last heard from, three years after operation, she was in good health.

Case 3. W. T., a 46 year old man, was admitted to the chest service with a history of productive cough for one year and fever, pain, and hemoptysis for three months. Physical examination showed massive atelectasis of the left upper lobe and a bronchogram revealed a block of the left upper lobe bronchus. The diagnosis of a bronchiogenic carcinoma was made and a total pneumonectomy was performed (individual ligation). The patient's postoperative course was complicated by the development of an empyema, a bronchial fistula, pericarditis, and auricular fibrillation on the fourth postoperative day. The patient was given digitalis and quinidine sulfate with return to sinus rhythm. Subsequently auricular flutter developed transiently. The patient was finally discharged in only fair condition and, according to a communication from his family, died three months after operation from heart failure.

Case 4. H. W., a 44 year old male, was admitted with a history of productive cough and weight loss for one year and pain and dyspnea for four months. Physical examination showed a right upper lobe atelectasis and bronchogram revealed a block of the right upper lobe bronchus. The diagnosis of bronchiogenic carcinoma was made, and a total pneumonectomy was performed (individual ligation). The patient's postoperative course was complicated by the development of auricular flutter with 2:1 and 3:1 block on the third postoperative day and also by the development of an empyema. The arrhythmia disappeared without specific medication on the seventh postoperative day. The patient was discharged and when last contacted, one year later, was in good health.

Case 5. L. T., a 57 year old man, was admitted to chest service complaining of a productive cough, hemoptysis and weakness for one month. Physical examination and bronchoscopy showed a block of the left lower lobe bronchus. The diagnosis of bronchiogenic carcinoma was made and a total pneumonectomy was performed (individual ligation). The patient developed auricular flutter with 2:1 block on the third postoperative day. The arrhythmia after treatment with digitalis changed to

auricular fibrillation and finally to a sinus rhythm. When heard from four months after discharge the patient was in good condition.

Case 6. E. S., a 59 year old man, was admitted to chest service with right universal bronchiectasis which involved particularly the middle and lower lobes. A total pneumonectomy was performed by the individual ligation method. Postoperatively the patient developed an empyema and auricular flutter with 2:1 and 1:1 block on the second postoperative day and within two hours was in moribund condition with extreme heart failure. The cardiac glycoside, k-strophanthin, in the dose of 1.5 mg. was given in maintenance doses and reversion to sinus rhythm occurred on the fifth postoperative day. Later the patient was discharged in excellent condition without cardiac symptoms. He was seen again six months later and was found to be in good health.

Case 7. F. T., a 67 year old female, was admitted to the hospital with a history of dry cough, weakness and dyspnea for six months. Physical examination showed an atelectasis of the left upper lobe and bronchogram together with bronchoscopic examination revealed a block of the left upper lobe bronchus. A total pneumonectomy was performed (individual ligation). On the second postoperative day the patient developed auricular fibrillation which lasted for three days and disappeared without medication. The patient was discharged in excellent condition and at last report, two years later, was enjoying good health.

Case 8. L. H., a 53 year old man, was admitted to the hospital complaining of cough and hemoptysis for six months and dyspnea and weakness for three months. Physical examination showed an atelectasis of the left upper lobe and the bronchogram revealed a block of the left upper lobe bronchus. The diagnosis of bronchiogenic carcinoma was made and a total pneumonectomy was performed (individual ligation). The patient developed auricular fibrillation on the fifth postoperative day which did not improve in spite of digitalis administration for 17 days. The patient was discharged but returned to the hospital six months later with the auricular fibrillation still present. At this time digitalis was tried again with some improvement in his heart condition but the arrhythmia persisted.

Case 9. N. M., a 39 year old man, was admitted to chest service with a history of a productive cough and hemoptysis for seven months and weakness and weight loss for three months. Physical examination revealed an atelectasis of the middle and lower lobes on the right. Bronchoscopic examination showed a tumor mass extending into the right middle and lower lobe bronchi. The diagnosis of bronchiogenic carcinoma was made and a total pneumonectomy was performed (individual ligation). The patient made an uneventful recovery with the exception of the development of auricular fibrillation on the seventh postoperative day. At this time he was fully digitalized and two days later normal sinus rhythm was restored. The patient was discharged without any cardiac symptoms.

Discussion

The cause of the development of the arrhythmias following pneumonectomy remains obscure although precipitating factors appear to be involved in some of the cases. Age appears to be an important predisposing element with the older age group showing the higher incidence of this complication. Consideration of other possible associated etiologic and anatomic influences gives no direct clue as to why certain patients undergoing the arduous procedure of pneumonectomy do develop such cardiac disturbances and others do not. As is commonly known these arrhythmias may be precipitated by

any sudden effort, nervous excitement, trauma or surgical procedures. Fundamentally in the background there is always the potentiality of the individual's inherent physiologic nervous reactability to these sudden stresses and strains initiating the mechanism leading to the production of the abnormal cardiac rhythms. In studying the natural history in the general population of the development of auricular fibrillation and auricular flutter which are the more important of the arrhythmias encountered in this study, usually one finds in the background definite evidence of heart disease, although sometimes the individual so affected may not present any detectable derangement. As stated previously, however, in this study no correlation was noted between prior heart involvement and subsequent cardiac abnormalities. Sudden compensatory emphysema in the remaining lung should be considered as a potential factor, in the production of the arrhythmias but against this possibility is the lack of evidence of a significant amount of post-operative emphysema developing, and the absence in the first place of any close association between emphysema and cardiac arrhythmias.

The most likely reason for the high incidence of arrhythmias following pneumonectomy has been suggested by an experimental study reported by Smith and Wilson.[6] They pointed out that an auricle which has been rendered irritable by anoxemia may be precipitated into fibrillation through the effect of vagus nerve stimulation shortening the refractory period of the auricle and lessening conductivity. From the clinical point of view there is a strong suggestion that in heart disease which is attended by reduced coronary artery flow and anoxemia of the myocardium, normal vagal stimuli might be amplified in their effects upon the heart, leading in some cases to the establishment of auricular arrhythmias. Certainly the common occurrence of auricular fibrillation in coronary artery disease, myocardial infarction and congestive heart failure is well known. From this and other clinical experimental evidence it appears very logical to conclude that the two factors of anoxemia and vagal stimulation act synergistically in the production of abnormal cardiac rhythms. In the procedure of total pneumonectomy a certain degree of anoxemia very likely occurs, although every attempt is made to reduce the extent of anoxemia by means of routine use of oxygen administration postoperatively. The factor of vagal stimulation occurs indirectly to a greater or smaller degree as a result of the extensive thoracic manipulation necessarily involved in total pneumonectomy.

In treating the patient who develops an arrhythmia, the physician and surgeon have to decide whether special treatment should be given to control the ventricular rate or whether it is preferable to wait for possible spontaneous reversion to a normal sinus rhythm as may occur in many instances simply with the help of morphine or other forms of sedation. This important decision must always be based on the condition of the patient since immediate specific therapy in serious cases may be either life saving or at least necessary to allay congestive heart failure. Rapid digitalization in

such instances is then indicated. In case there is imminent danger such as occurred in Case 6 where rapid auricular flutter resulted in profound cardiac failure after only a few hours, intravenous use of a cardiac glycoside such as lanatoside-C, or K-strophanthin may mean the difference between life and death. If there is no immediate danger, one may give either digitalis by the oral route, or quinidine sulfate, or even both depending upon the individual circumstances of the case. The important fact to point out, however, is that the patient's cardiac rhythm must be carefully and frequently observed during at least the first postoperative week in order to determine at the earliest possible moment the onset of abnormal heart action and thus permit early decision as to the therapeutic procedure of choice. In addition, since in such patients from whom a lung has been removed, breathing is loud and stertorous and the bronchial and tracheal noises usually sufficiently pronounced to drown out the cardiac sounds, it is advisable to take frequent postoperative electrocardiograms in order to check accurately the cardiac rhythm by objective means, to recognize a hitherto unsuspected auricular flutter, and to aid in the management of the patient once the arrhythmia has developed.

Summary

Arrhythmias are among the chief cardiac complications encountered following total pneumonectomy and occurred in 9.1 per cent of the entire series of 120 patients studied and in 14.3 per cent of those over 35 years of age. The arrhythmias included five instances of auricular fibrillation, four of auricular flutter and one each of frequent auricular and ventricular extrasystoles.

Apart from the factor of age, the reason for the high incidence of arrhythmias following pneumonectomy could not be definitely determined. It is suggested that anoxemia and vagal stimulation may act synergistically in the production of these abnormal cardiac rhythms.

Constant observation must be maintained for early recognition of the occurrence of abnormal cardiac rhythms. Treatment should be directed primarily to the attainment of prompt restoration of a normal sinus rhythm, and this result may be most often accomplished by rapid intravenous digitalization.

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RHEUMATOID SPONDYLITIS: A STUDY OF 1,035 CASES *

By Howard F. Polley, M. D., and Charles H. Slocumb, M.D.,
Rochester, Minnesota

Study of more than 1,000 cases of rheumatoid spondylitis encountered at the Mayo Clinic has yielded data which may help to clarify certain aspects of this disease and may help the physician to answer a few of the questions frequently asked concerning the condition. The erythrocyte sedimentation rate and the roentgenographic findings in cases of rheumatoid spondylitis also will be discussed briefly.

Sex, Age at Onset, Symptoms and Course

What is the incidence of this disease in men as compared to women? In our series there was a total of 931 men and 104 women. The ratio of men to women was 9:1. Seven hundred forty-nine patients had rheumatoid spondylitis without peripheral rheumatoid arthritis. There were 671 men and 78 women; a ratio of 9:1. Two hundred eighty-six patients had peripheral rheumatoid arthritis associated with rheumatoid spondylitis; 260 were men and 26 were women; a ratio of 10:1. These ratios are essentially the same as for the group as a whole.

What is the age at onset in this disease? The distribution of cases in this series according to the age at onset of symptoms is shown in table 1. Symptoms of 80 per cent of patients first appeared when they were between the ages of 15 and 35 years. The average age at the onset of symptoms in this series was 26.7 years. The age at the onset of symptoms in men and women did not show any significant variation from the average.

What is the location of initial symptoms of rheumatoid spondylitis? The first symptoms were most frequently in that part of the pelvis, lumbar and thoracic regions known as the torso (table 2). In about half of these cases (359 cases) the lower part of the back or lumbar region was specified. In 124 cases the onset of symptoms was in the region of the hip and in 100 the disease was first manifested by sciatica. The first symptoms were referable to the thoracic region in 60 cases and the specific part of the back could not be localized in 100. The first symptoms appeared in the neck and shoulder girdle in only 3.4 per cent of the cases (35 cases). These data seem to indicate that it is uncommon for symptoms of rheumatoid spondylitis to begin in the neck and only seldom do they begin in the thoracic region and pursue

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a descending course. In most of the cases then the spinal symptoms of the disease follow an ascending course; they begin in the lower part of the back and extend upward.

Symptoms in peripheral joints are sometimes an initial manifestation of rheumatoid spondylitis. They were found in 242 or 23 per cent of the cases in this series. The average age of these patients is slightly less than that of the group as a whole, 24.7 years as compared to 26.7 years. Symptoms referable to peripheral joints were polyarticular in 87 per cent of cases and monarticular in 13 per cent. There seemed to be a marked predilection for involvement of joints of the lower extremity in this phase of rheumatoid spondylitis. Joints of the lower extremities other than the hip were involved

TABLE I

Age at Onset of Symptoms

Age, yrs.	Cases
Less than 20	244
20–29	518
30–39	170
40 or more	86
Total	1,018*

* In 17 cases age at onset of symptoms was indeterminate.

TABLE II

Location of First Symptoms

Torso		743
Lower back; lumbar region	359	
Hips	124	
Sciatic region	100	
Thoracic region	60	
Back, not localized	100	
Neck and shoulder		35
Peripheral joints		242
Miscellaneous		15
Total		1,035

in two thirds of the 242 cases (65 per cent). In most of the remaining cases (31 per cent) joints of both the upper and lower extremities were involved, and joints of the upper extremities alone were involved in 4 per cent of the cases. There was no apparent residual damage of the peripheral joints in 50 per cent of the 242 cases. Symptoms referable to peripheral joints at the onset of rheumatoid spondylitis did not predispose to involvement of peripheral joints later during the course of the disease.

What is the course of the symptoms in rheumatoid spondylitis? In 72 per cent of the cases studied exacerbations and remissions were a characteristic feature of the course of this disease. In 28 per cent a fulminating progressive course without any remissions occurred. This feature of the symptomatology is maintained regardless of the location of the initial symptoms.

What is the predictable duration of the disease? Unfortunately, this is a question which cannot be answered for an individual patient. The length

of time symptoms had been present prior to examination at the Mayo Clinic is shown in table 3. Symptoms had been present for 20 or more years in 74 cases. The average duration of symptoms prior to our examination was 8.5 years. This does not indicate the average duration of the disease by any means but it serves as a basis for evaluating certain features of the course of the disease as it occurred in this study.

What is the possibility of the disease being limited to spinal involvement? or, What is the incidence of arthritis in special regions during the course of rheumatoid spondylitis? Limitation of motion in the cervical portion of the spinal column was noted in 45 per cent of cases in this series after an average duration of symptoms of eight and one half years. Transitory symptoms in the region of the neck had been present in an additional 12 per cent of the cases. Involvement of the hip joints was noted in 28 per cent of

TABLE III

Duration of Symptoms at Examination at Clinic

Years	Cases
Less than 5	311
5–9	242
10–14	201
15–19	90
20 or more	74
Total	1,018*

* In 17 cases duration of symptoms was indeterminate.

cases. The joint damage was bilateral in three fourths of these cases. Arthritis of the hip and shoulder or the so-called root-joint involvement has at times been regarded as a characteristic feature of rheumatoid spondylitis. Although this association was noted in a fourth of the cases in this group, it occurred in only 7 per cent of all the cases studied. Patients having initial symptoms of rheumatoid spondylitis referable to the region of the hips showed no increased incidence of arthritis of the hip joints.

Involvement of peripheral joints producing residual damage of joints at the time of our examination was noted in 28 per cent of cases. Transitory symptoms were described in an additional 22 per cent of the cases. Thus, it might be said that symptoms referable to peripheral joints will occur in one half of the cases of rheumatoid spondylitis but in only a fourth of the cases will it lead to chronic, residual articular damage. When involvement of the peripheral joints does occur under these circumstances, the chances are it will be monarticular in a third of the cases.

Sedimentation Rate

Estimation of the sedimentation rate is a procedure frequently used as an aid in evaluating rheumatic symptoms. The sedimentation rate was less than 40 mm. in the first hour (Westergren method) in slightly less than half of the cases (table 4). In an additional 28 per cent it was from 40 to 59 mm. making about three fourths of the cases in which it was less than 60 mm. In the remaining cases the sedimentation rate varied from 60 to more than 100 mm. We wish to emphasize that the sedimentation rate was normal in 176 cases or nearly a fifth of the cases. It would seem that the sedimentation rate does not tend to be as high in rheumatoid spondylitis as it is in peripheral rheumatoid arthritis, although at times high readings may be seen in the former.

TABLE IV

Sedimentation Rate
(Westergren Method)

Mm. in 1 hr.	Cases	Per Cent
Less than 20	176	19
20–39	254	27
40–59	264	28
60–79	133	14
80–99	79	8
100 and more	43	4
Total	949	100

Roentgenologic Manifestations

Roentgenologic evidence of rheumatoid spondylitis may be lacking if the progress of the disease has not resulted in destruction of cartilage and subchondral bone. When present, the characteristic roentgenologic findings in rheumatoid spondylitis are arthritis of the sacro-iliac and apophysial joints, calcification or ossification or both of spinal ligaments and osteoporosis of vertebrae. The so-called bamboo spine has in the past been regarded as the characteristic roentgenologic evidence of rheumatoid spondylitis but the changes seen in sacro-iliac joints are equally characteristic and occur much earlier.

Involvement of the sacro-iliac joints in rheumatoid spondylitis is typically bilateral. In this study bilateral sacro-iliac arthritis occurred in 98 per cent of the cases, an example of which is shown in figure 1*a*. The patient, a man 23 years of age, had had low back pain and sciatica which affected first one side and then the other for two years. Blurring and irregularity of the

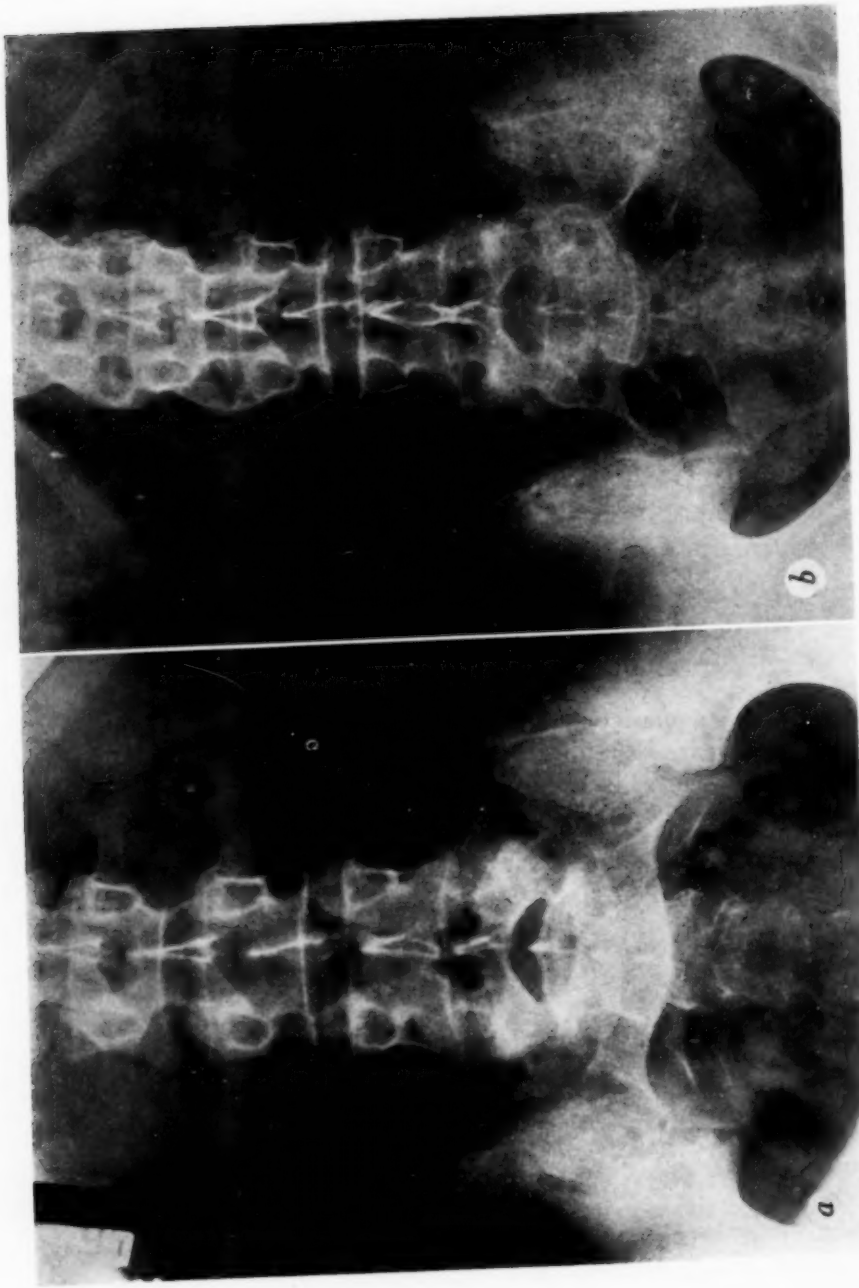

FIG. 1. Bilateral sacro-iliac arthritis characteristic of rheumatoid spondylitis; *a*, on first admission; *b*, 10 years later. There is evidence at this time of ligamentous calcification in the lumbar region. The sacro-iliac joints are nearly obliterated.

later. There is evidence at this time of ligamentous calcification in the lumbar region obliterated.

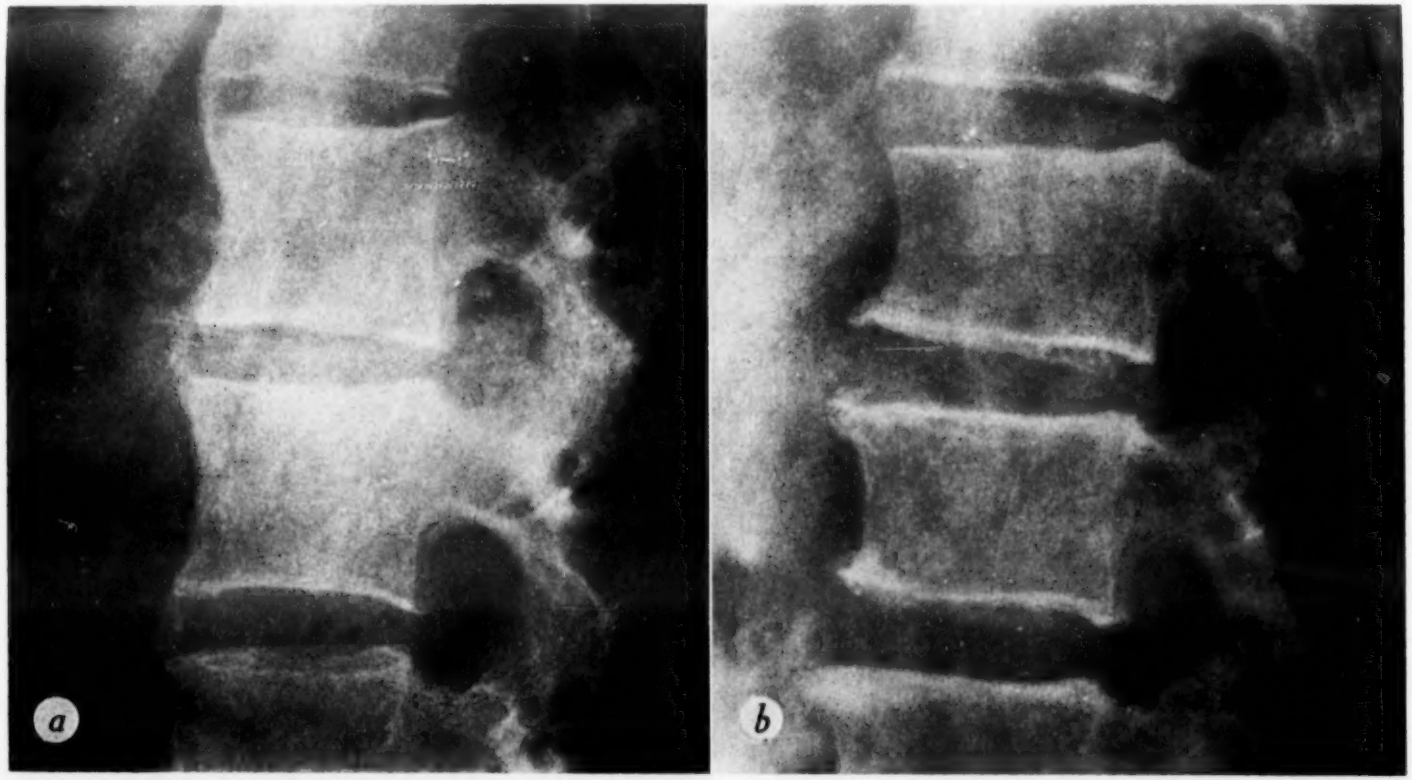

FIG. 2*a*. The lumbar portion of the spinal column in a case of rheumatoid spondylitis showing calcification of the anterior spinal ligament. This is to be contrasted with *b*. *b*. The osteophyte of osteo-arthritis in the lumbar part of the spinal column. See also figure 3 and text.

joint surface due to an actual destructive arthritis and marginal sclerosis of both sacro-iliac areas may be seen.

Arthritis of apophysial joints undoubtedly occurs as a significant part of the disease process but it is often difficult to demonstrate roentgenologically. Calcification of spinal ligaments may be present at the time of the first symptoms but it is more often demonstrable only after months or years of the disease. It was not evident in the roentgenogram shown in figure 1*a* which was made when the patient was first seen. However, when he was reëxamined 10 years later, after he had had symptoms for 12 to 13 years, the roentgenogram revealed the ligamentous calcification characteristic of rheumatoid spondylitis (figure 1*b*). The sacro-iliac joints were nearly obliterated.

The ligamentous changes seen in rheumatoid spondylitis are usually distinct and should not be confused with the changes of osteo-arthritis of the spinal column. A roentgenogram of the lumbar part of the spinal column in a case of rheumatoid spondylitis is shown in figure 2*a*. Calcification of

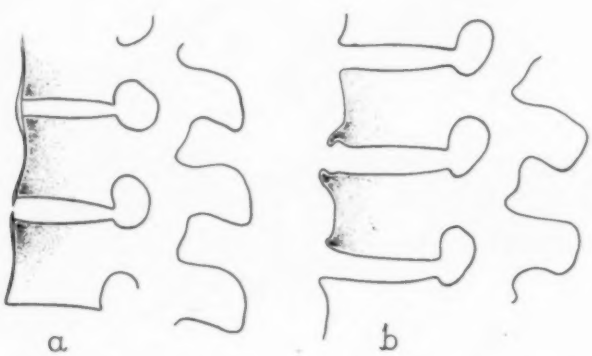

FIG. 3. Diagrammatic representation of roentgenograms shown in figure 2*a* and *b*.

the anterior longitudinal ligament is incomplete in one region but has progressed to bridging of two of the vertebrae in another region. A calcified spinal ligament is seen as a thickening of homogeneous density superimposed on the surface of the vertebra and spanning a normal intervertebral space. For comparison a roentgenogram of the lumbar vertebrae in a case of osteo-arthritis showing spur formation in several areas is included (figure 2*b*). The osteophyte has a variation in density, and cortex and cancellous bone may at times be as clearly differentiated as in the body of the vertebra.

The same conditions are diagrammatically represented in figure 3. Figure 3*b* shows the bony spur or osteophyte which is an outgrowth of the vertebral body; and figure 3*a* shows the calcified ligament, in close apposition to the vertebra but superimposed on it rather than being a part of it.

Unilateral sacro-iliac arthritis suggests the presence of a specific infectious disease, such as tuberculosis, but it may occur infrequently in rheu-

matoid spondylitis. It was noted in six cases in this study, an example of which is shown in figure 4. Symptoms of rheumatoid spondylitis had been present for 10 years before figure 4 was made. Marginal sclerosis and destruction of the right sacro-iliac joint but no apparent involvement of the left sacro-iliac joint may be noted in the roentgenogram. In the lumbar region there is marked evidence of calcification of spinal ligaments.

FIG. 4. Unilateral sacro-iliac arthritis in a patient who had had rheumatoid spondylitis for 10 years. Calcification of spinal ligaments in the lumbar region is marked.

Absence of roentgenologic evidence of involvement of the sacro-iliac joints is unusual in rheumatoid spondylitis but it does occur. It was found in nine cases in this study. In the case, the roentgenogram of which is included, symptoms of rheumatoid spondylitis had been present for seven years prior to examination at the clinic (figure 5*a*). In this case too, fusion of the laminae of the second, third, fourth and fifth cervical vertebrae occurred (figure 5*b*).

The negative or unilateral sacro-iliac joint changes which may be seen in cases of rheumatoid spondylitis, however, do not detract from the significance of the 98 per cent of cases in which the changes are bilateral. It is advisable

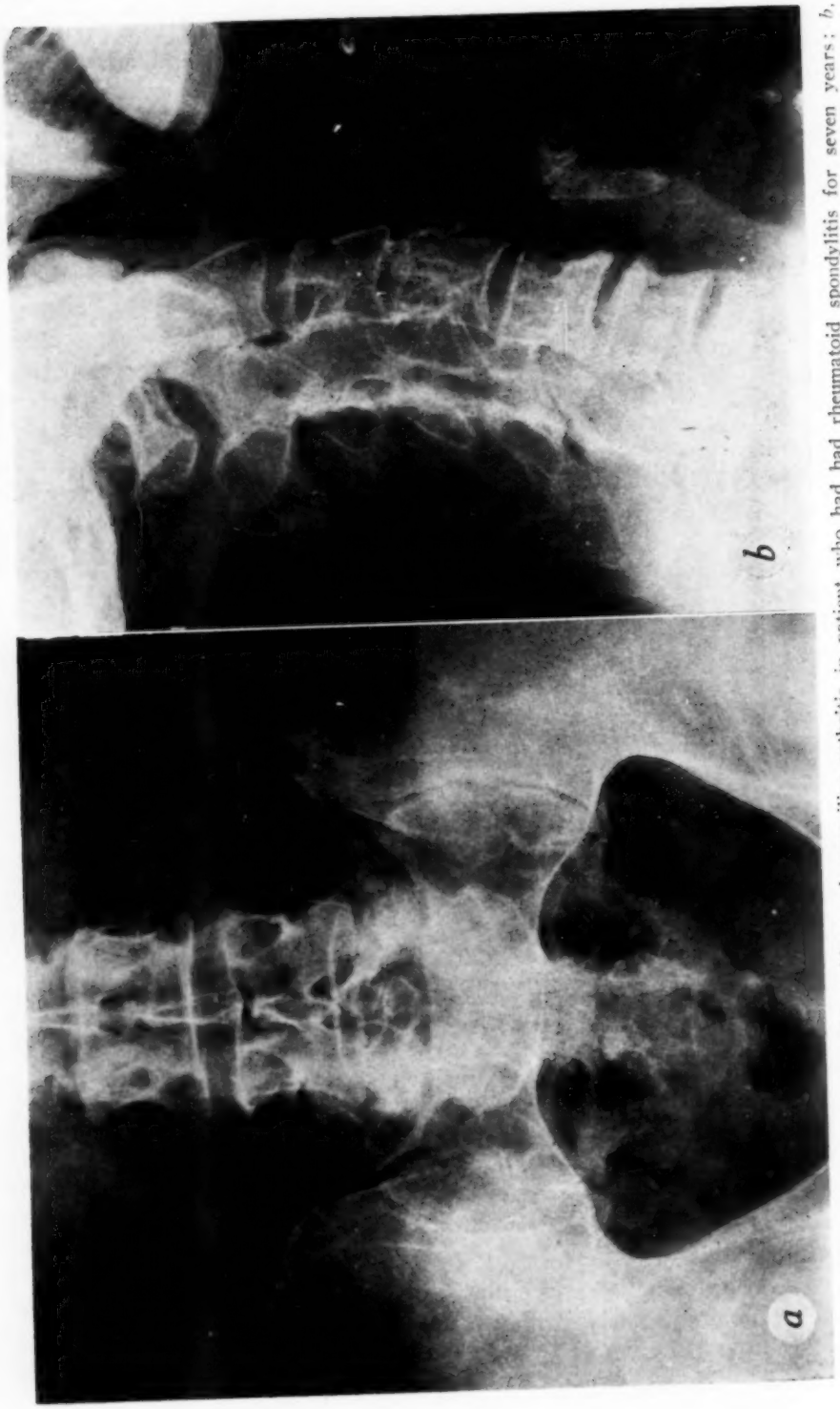

FIG. 5a. Absence of roentgenographic evidence of sacro-iliac arthritis in patient who had had rheumatoid spondylitis for seven years; *b*, fusion of the laminae of the second, third, fourth and fifth cervical vertebrae in same case as *a*.

to make roentgenograms of the sacro-iliac joints as well as the painful part of the spinal column in all cases in which rheumatoid spondylitis is considered in the differential diagnosis.

Comment

For at least some of the other questions which might be asked about rheumatoid spondylitis the answers are less easily obtained and perhaps less satisfactory. We hope that further study will produce more information of value to the understanding of this disease.

Fig. 5a. Absence of roentgenographic evidence of sacro-iliac fusion of the second, third, fourth and fifth cervical vertebrae in same case as

TRICHINOSIS: REPORT OF AN EPIDEMIC *

By Frederick H. Hathaway, Capt., M.C., A.U.S., and Lamson Blaney, Capt., M.C., A.U.S.

Trichinosis is an acute disease usually occurring in man following the ingestion of pork products infested with the encysted larvae of the Nematode, *Trichinella spiralis*. The illness is characterized by fever, muscular pains, swollen eyelids, and a variable course, depending on the degree of infestation. The adult forms of the parasite (male and female) develop in the intestinal tract where the female deposits her eggs after penetrating the mucosa. In a few days the young *trichina* enter the intestinal lymphatics and are then transported by the circulatory system to all parts of the body. Usually, the initial symptoms of the disease are gastrointestinal and occur during the first week after ingestion of trichinous meat. Following this there is a period of toxicity corresponding with the migration of the larvae throughout the body. Finally, there is a period of larval encystment in muscle tissue during which time the patient either recovers from the disease or continues on to cachexia and death.

Report of the Epidemic

The present report is concerned primarily with 83 German prisoners of war who were hospitalized for trichinosis at an A.A.F. Regional Station Hospital. Their ages varied from 18 to 41 years with an average age for the group of 25.5 years. Eighty-two patients were admitted between Dec. 28, 1945 and Jan. 28, 1946. One patient, admitted on Dec. 19, 1945, with the diagnosis of cellulitis of the hand, later developed trichinosis (Jan. 1, 1946) in the hospital. One individual who had been transferred to the prison compound from another installation had his first meal in the prison mess on Dec. 20, 1945. This man noted initial symptoms of trichinosis on Jan. 15, 1946. The length of hospitalization for the entire group ranged from 19 to 48 days with an average hospital stay of 26 days.

All of these patients were members of a detachment of 587 prisoners confined in a nearby prison compound where they prepared and served their own food. The mess hall was opened on Dec. 4, 1945. The meat, which was supplied by the Quartermaster, was identical with that furnished troops stationed at the post. All meat used came from Federally inspected plants and in addition was inspected by the Veterinary Corps of the U. S. Army. This meat included raw pork sausage, supplied in the form of 10 lb. rolls, in quantities sufficient to last approximately two days. A check revealed that sausage was issued by the Quartermaster to the prisoners

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mess only on the following dates: Dec. 6, 7, 9, 17, 19, and 26, 1945. On Dec. 28, 1945 a sufficient quantity was issued to last through Jan. 1, 1946. Sausage appeared on the menu at the prison mess approximately three times weekly and was usually served uncooked. Questioning of the patients revealed that the ingestion of raw pork is widely prevalent in Germany, especially in the northern portions. That this is a relatively safe practice there may be gathered from the statistics cited by Gould[1] which stated that the proportion of hogs with trichinous infection in Germany was approximately 0.001 per cent. In Berlin between the years of 1883 and 1924 no case of human trichinosis was reported after the eating of pork that had passed

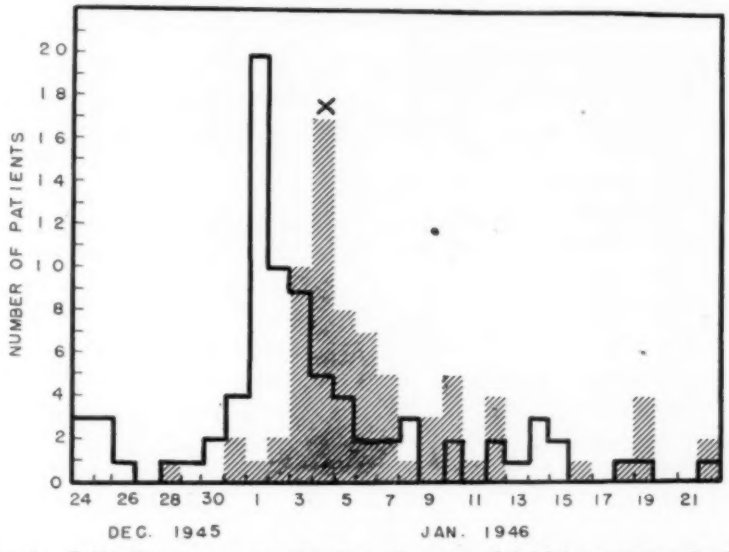

CHART 1. Solid line represents the date of onset of initial symptoms in 83 patients hospitalized with trichinosis. Shaded area represents the admission dates of 75 patients. (Two patients were admitted prior to December 24, 1945 for other conditions and subsequently developed trichinosis in the hospital. Six not included in chart were admitted between January 22 and 28, 1946.)

(X)—Indicates date after which no improperly prepared meat was served in the prison mess (Jan. 4, 1946).

microscopic inspection. In the United States, where the incidence of trichinosis in hogs is approximately 1.5 per cent, the individual is protected only by adequate cooking of all pork products.

The first few patients in this series were admitted to the hospital with a diagnosis of nasopharyngitis, sinusitis, and malaria. However, the presence of eosinophilia and swollen eyelids suggested that a more proper diagnosis was trichinosis. Steps were immediately taken to prevent any further serving of uncooked meat. Since these prisoners ate only food prepared in their own mess, with the exception of a few who occasionally ate at their place of work, there is no doubt that the source of infection in this epidemic was the uncooked sausage served during the month of December, 1945.

In this series the dates of onset ranged from Dec. 24, 1945 to Jan. 22, 1946 (chart 1). In explaining the rather wide spread of dates of onset several factors must be considered. First, it is improbable that all the pork eaten was trichinous; second, the amount eaten per man varied. Twelve men in this series gave a history of having eaten more than the "usual" amount. Some obtained second servings, while others who were kitchen workers ate double the "usual" amount. Third, gastrointestinal complaints as the initial symptoms occurred in only 29 individuals (34.9 per cent) and were mild in nature. Many were unaware of their illness until the onset of fever, swollen eyelids and headache.

Symptomatology

Symptoms of those individuals hospitalized were generally similar, varying only in degree of severity (table 1). All patients, at the onset of their illness, complained of fever, headache, and malaise. Headaches were of

Table I

Frequency of Symptoms as They Occurred in 83 Patients Hospitalized for Trichinosis

	Number	%
Total no. patients	83	
General symptoms		
Fever	83	100
101° or more	62	74.7
Less than 101°	21	25.3
Headache	83	100
Malaise	83	100
Muscle pain	77	92.8
Muscle pain with tenderness	48	57.8
Swollen eyelids	72	86.7
Dryness of mouth	54	65.1
Profuse sweating	38	45.8
Chills	10	12.1
Epistaxis	10	12.1
Diplopia	6	7.2
Gastrointestinal	29	34.9
Abdominal discomfort	14	16.9
Diarrhea	12	14.5
Nausea	6	7.2
Constipation	6	7.2
Vomiting	3	3.6

varying severity and duration, usually frontal in location, and most severe during the febrile period of the disease. In some individuals headaches persisted intermittently into convalescence. Moderate to severe malaise occurred in 55 (66.3 per cent) and lasted three to 30 days with an average of 15 days. The remainder (28 men) had mild malaise varying from two to 18 days with an average duration of nine days. Most of the patients remained in bed during the period their temperatures were higher than 100° F. Later, they tired easily with moderate activity on the ward and often

complained of excessive fatigue after performing ward "kitchen police." Nine patients still complained of mild fatigue at the time of discharge.

Swollen eyelids as seen on physical examination or reported in the history were noted in 72 or 86.7 per cent of the men hospitalized. Usually, the swelling subsided in three to five days.

Muscle pain was an outstanding complaint and occurred in 77 patients (92.8 per cent). Of this group 48 (57.8 per cent) had associated tenderness. Muscle pains were distributed roughly in the following areas: neck, upper extremities, lower extremities, and other areas; i.e., back, intercostals, abdominal, and ocular. It was found that 40 men (48.2 per cent) had pain involving three or more of these areas.

Profuse sweating, especially following any activity, occurred in 38 (45.8 per cent). Dryness of the mouth was a complaint in 54 men.

Chilliness was commonly associated with the onset of the disease and in 10 instances frank shaking chills were reported.

Recurrent epistaxis occurred in 10 men early in the disease. Diplopia coincident with swollen eyelids was reported by six patients.

Gastrointestinal complaints were not prominent in this epidemic. There were only three patients admitted primarily for this type of complaint. One of these patients was admitted for right lower quadrant pain which occurred 10 days after an episode of fever, swollen eyelids, and headache. A second had persistent nausea and vomiting. The third was admitted complaining of severe generalized abdominal pain and in addition had a temperature of 105° F. Histories taken on admission, however, revealed that gastrointestinal symptoms had occurred within the two-week period prior to admission in 29 (34.9 per cent). Of this number, 14 had had abdominal discomfort of varying degree and the remainder had noted diarrhea, constipation, or nausea with vomiting. Anorexia was a prominent feature in the entire series.

Physical Findings

The patients were all well nourished German prisoners of war who worked as laborers and translators. On admission none of the patients appeared seriously ill. The most significant physical finding was edema of the eyelids. Injection of the conjunctiva was present in 19 of the patients while hemorrhages of the bulbar conjunctiva were found in three, bilaterally in two and unilaterally in one. Examination of the fundi in all but four patients revealed only the incidental presence of a healed chorioretinitis in one and a congenital angioma of the left inferior temporal vein in another.

Lymph glands were palpable and often tender in 25 (30.1 per cent) of the patients. The finding varied from enlargement of a few posterior cervical glands in the majority to generalized lymphadenopathy of mild degree in four.

The spleen was palpable in four instances. One of these patients gave a

past history of malaria, another a history of infectious hepatitis in 1943. The spleen was tender in one of the remaining two.

An erythematous macular rash appeared in two patients. This faded the same day in one and recurred for several successive evenings in another. A few complained of transitory itching of the skin during the toxic phase. Two patients had firm, slightly tender, subcutaneous nodules measuring approximately 1 cm. in diameter which were present for about one day.

Mydriasis was noted in 15 patients (18.1 per cent). Their pupils measured more than 5 mm. in diameter early in the disease and returned to normal during convalescence.

Every patient in this series had a temperature higher than normal at some time during his illness. Sixty-two (74.7 per cent) had temperature elevations of 101° F. or higher and among these the highest recorded was 105° F. These temperatures were of a remittent type in 41 patients and of an intermittent type in 21. The duration of temperatures over 101° F. varied from one to 10 days with an average duration of one week. There was no significant difference in the height and duration of these two types of fever. These higher temperatures often were followed by the irregular, low grade, afternoon elevations which were common for the remaining 21 patients in this series. In some instances irregular, low grade, afternoon temperatures persisted for two to three weeks.

Laboratory Findings

During his hospital stay each patient averaged having 2.8 leukocyte counts and differential blood smears. Of the 83 patients hospitalized it was found that 69 or 83.1 per cent had leukocyte counts ranging higher than 10,000 per cu. mm. at some time during their illness. Of this number the highest counts recorded fell between 10,000 and 15,000 per cu. mm. in 52 patients (62.6 per cent); between 15,000 and 20,000 per cu. mm. in 13 patients; and above 20,000 per cu. mm. in five individuals. The highest count recorded was 28,000 per cu. mm. Finally, there was a group of 14 patients (16.9 per cent) whose white blood cell counts were always within normal limits (5,000 to 10,000).

In a total of 237 blood smears done on hospitalized patients it was found that 107 or 45 per cent showed eosinophilia ranging from 20 to 40 per cent inclusively. The other blood smears (130) showed eosinophilia of greater or lesser degree. The highest recorded eosinophilia was 61 per cent. No significant trend of eosinophilia was noted except for slightly lower counts in any given individual at the beginning and end of hospitalization. There was no relationship noted between the height of eosinophilia and the height of the leukocyte count.

The sedimentation rate in 70 patients was determined for the first time during the second and third weeks of illness and was repeated in several instances. The distribution of the highest sedimentation rate attained by

each patient was such that 41 (54.7 per cent) were within the normal range for males, i.e., 15 mm. per hour by the Westergren method. The sedimentation rates in 34 (45.3 per cent) were above that figure. Generally, the sedimentation rate returned to normal levels during convalescence in those patients showing elevated values.

TABLE II

Relationship of Eosinophilia to White Blood Count in a Representative Group (32) Selected from 83 Patients with Trichinosis. Week of Illness Calculated from Onset of Initial Subjective Symptoms

Case #	1st Week		2nd Week		3rd Week		4th Week		5th Week	
	W.B.C.	% Eosinophilia	W.B.C.	% Eosinophilia	W.B.C.	% Eosinophilia	W.B.C.	% Eosinophilia	W.B.C.	% Eosinophilia
1	7,000	1	9,950	36	9,100	4				
2			8,350	16			7,650	40		
3			7,000	55	8,850	26				
4	7,450	9	9,750	30	8,500	24				
5	9,100	0	9,400	26			9,700	14		
6	7,550	16	18,700	40			9,000	25		
7	7,300	1	11,500	50	8,500	25				
8	7,950	35	9,600	42	12,200	53				
9	11,700	53	14,150	39	14,500	41				
10	10,500	21	11,100	25	11,500	1				
11	12,000	24	7,400	30	6,050	35	8,800	23		
12	10,500	20	14,500	30	12,900	25				
13	10,400	34	6,800	26			12,600	29		
14	12,300	30	14,500	51					11,500	25
15	7,850	24	12,500	33			11,200	35		
16			8,500	25	12,350	40	11,900	38		
17	7,200	34	14,200	23			10,200	24		
18	7,800	30	13,500	25			10,100	25		
19	7,850	24	12,000	25	14,600	33				
20	6,300	18	9,350	29			11,550	39	11,050	25
21	7,200	11	12,750	38	10,950	28			10,950	15
22	5,250	10	9,850	39	11,400	17			4,800	2
23	9,500	24	10,650	39	12,350	37				
24	7,200	18	8,150	28					10,100	12
25	10,800	30	10,500	50			7,200	29		
26	9,850	40	11,150	36			7,400	27		
27	5,050	5	5,250	23	11,550	43	19,900	23		
28	11,400	0	16,450	20	16,400	18	11,200	25		
29	9,800	0	12,750	41			18,000	32	17,800	25
30	8,400	12	12,400	40	15,050	33			5,900	33
31	10,300	3	22,100	11	27,050	31	18,850	20	14,500	12
32			21,150	44	12,500	30	15,800	27		

In 14 cases a trace of albumin was found in the urine during the febrile period of the disease. In all but two of these the temperatures had reached 102° F. or higher.

The stools of several patients giving a history of diarrhea were examined, but in none were there significant findings.

SKIN TESTS

Intracutaneous skin tests were performed with a commercial type of Trichinella Extract (Eli Lilly & Co.) upon 80 patients (table 3). The

extract was a 1:10,000 dilution. The time of the test varied from five to 40 days after the onset of initial symptoms, 75 being performed on or after the thirteenth day of symptoms. The test site (volar aspect of forearm) was examined for an immediate positive skin reaction within less than 30 minutes after injection of the extract. The presence of a blanched wheal, larger than that produced by the initial injection was interpreted as an immediate positive reaction. This area was often surrounded by an area of erythema, but in no instance were pseudopods observed. There were 28 (34.6 per cent) immediate reactors. In nine of these a papule persisted for

TABLE III
Results of Skin Tests Performed on 81 Patients with Trichinosis Using Commercial Trichinella Extract (1:10,000)

Total No. Tested—81			
Day of Illness	Imm. Pos. Reaction	Delayed Reaction	Negative Reaction
5th	1		
8th		2	1
11th		1	
12th		1	
13th	1	4	1
14th	2	6	
15th	5	11	1
16th	2	2	
17th	1		
18th	2	2	
19th	3		
20th	1	1	4
21st	2	1	1
22nd	2	4	1
23rd	1	1	1
24th	3	1	
25th		1	1
26th	1	1	
28th	1		1
36th		1	
40th			1
Total	28 (34.6%)	40 (49.4%)	13 (16%)

24 hours. Examination for a delayed reaction was made in 20 hours, at which time the presence of a red, slightly tender papule was regarded as positive. There were 40 (49.4 per cent) in this group. The remainder, or 13 (16 per cent) were negative. All control injections were negative. It is of interest to note that in one instance a test performed on the fifth day of illness resulted in an immediate reaction, but inasmuch as this man entered the hospital at a late date he probably became infected earlier than the onset of his symptoms would suggest. In a second, the test was negative when performed 40 days after the onset of symptoms of trichinosis. A third patient whose muscle biopsy was reported as showing interstitial myositis gave a negative reaction on the twentieth day of his disease.

Muscle Biopsies

Muscle biopsies were performed in 10 patients (table 4). The ones selected were those who seemed to fall most closely into the typical clinical picture as seen in this series of 83 individuals. The site of biopsy was at the point of maximum muscle tenderness in each patient. A time interval of three weeks from the onset of initial subjective symptoms was allowed before the biopsy procedure.

Table IV

Results of Muscle Biopsies in 10 Patients with Trichinosis Correlated with Their Respective Skin Tests

	Onset of Disease	Date of Biopsy	Site of Biopsy	Path. Findings	Results of Skin Tests
1	1/2/46	1/28/46	Biceps	Inter. myos.*	Imm. pos. react. on 19th day†
2	1/6/46	1/28/46	Gluteus max.	Inter. myos.	Imm. pos. react. on 15th day
3	1/2/46	1/28/46	Trapezius	Inter. myos.	Imm. pos. react. on 19th day
4	1/4/46	1/28/46	Biceps	Inter. myos. and larvae	Imm. pos. react. on 17th day
5	1/3/46	1/28/46	Gastrocnemius	Inter. myos.	Delayed react. on 25th day
6	1/1/46	1/28/46	Gastrocnemius	Inter. myos. and larvae	Imm. pos. react. on 20th day‡
7	1/8/46	1/28/46	Gastrocnemius	Inter. myos.	Negative on 20th day
8	1/3/46	1/28/46	Gastrocnemius	Inter. myos.	Imm. pos. react. on 18th day‡
9	1/3/46	1/28/46	Gastrocnemius	Inter. myos.	Delayed react. on 18th day
10	1/3/46	1/28/46	Gastrocnemius	Inter. myos.	Delayed react. on 18th day

* Interstitial myositis.
† Immediate positive skin reaction and day of disease.
‡ Immediate positive reaction persisted as a papule for 24 hours.

The muscle biopsies were studied by serial sections of the entire blocks of tissue. The pathological report was similar in each of the 10 specimens, and was as follows: "Sections show varying degrees of interstitial myositis. The cells in the exudate are largely plasma cells, but there are also numerous eosinophiles. Occasionally, there is found a collection of such cells plus macrophages and giant cells, which have the appearance of foreign body granuloma. In addition to these inflammatory changes there are changes in the muscle as well. Single fibers show atrophy and less frequently hypertrophy. In the rare hypertrophic fibers there is usually seen hyperplasia of the nuclei." In addition to the above findings larval forms of *Trichinella spiralis* were found in two instances.

The results of skin tests in the 10 patients who had biopsies performed (table 4) revealed that six gave immediate positive skin reactions, three gave delayed reactions and one had a negative skin test on the twentieth day of his illness.

The average hospital stay of patients who had biopsies was 37 days. It was felt that the procedure prolonged their expected stay by seven to 10 days, especially those in whom the site of biopsy was the gastrocnemius muscle. The other laboratory findings in this group did not vary significantly from those of the other hospitalized patients.

Treatment

Generally, treatment was symptomatic and supportive. Approximately 50 per cent of the patients received a saline laxative on admission but this did not alter their subsequent clinical course. One patient who was hospitalized on Dec. 19, 1945 for cellulitis of the hand received sulfadiazine, 1 gram every four hours, for four days (Dec. 19 to Dec. 23, 1945) and immediately following this a course of 300,000 units of penicillin was given over a period of 24 hours. However, on Jan. 1, 1946 he developed the symptoms of trichinosis which did not vary from the typical clinical picture observed in this series. A few other early admissions received sulfadiazine without demonstrable benefit. Another patient, who was hospitalized on Jan. 1, 1946 with a history of malaria, received atabrine in routine dosages for three days due to an erroneous laboratory report on his blood smear. This drug had no effect on his illness.

Complications and Associated Findings

At no time during their hospital stay were any patients considered seriously ill. No serious complications as a result of trichinosis were observed. Two individuals with complaints of abdominal pain were seen by the surgical consultant who felt that the complaints were associated with the primary disease, trichinosis.

Although headache of varying severity was present in every individual no meningeal signs or significant reflex changes were noted. One patient, on the tenth day of his illness, developed weakness of the right arm and leg with diminished pain sensation over the entire right side (midline distribution). Because there were no reflex changes noted and the condition cleared uneventfully in seven to 10 days it was felt that the episode was on the basis of a conversion reaction. Another patient had convulsive seizures which, after study by the psychiatric consultant, were said to be of an hysterical type. In one patient there was a recurrence of a rheumatoid arthritis which involved the left knee.

There were no cardiovascular complications noted. No deaths occurred in this epidemic. There were no patients hospitalized a second time for trichinosis during the two month period following the epidemic.

Study of Group Not Hospitalized

On Jan. 4, 1946 it became apparent that trichinosis was occurring in epidemic proportions. As previously stated, investigation revealed that

uncooked sausage had been served throughout December 1945. It was considered likely that each of the 587 prisoners had had an opportunity to ingest trichinous meat. Therefore, it was decided to obtain blood smears in order to ascertain the probable incidence of infection in this group as estimated by the degree of eosinophilia. The blood smears were taken on Jan. 10, 1946 while the prisoners attended evening mess. The men were divided into two groups, A and B (Chart 2). Group A was composed of

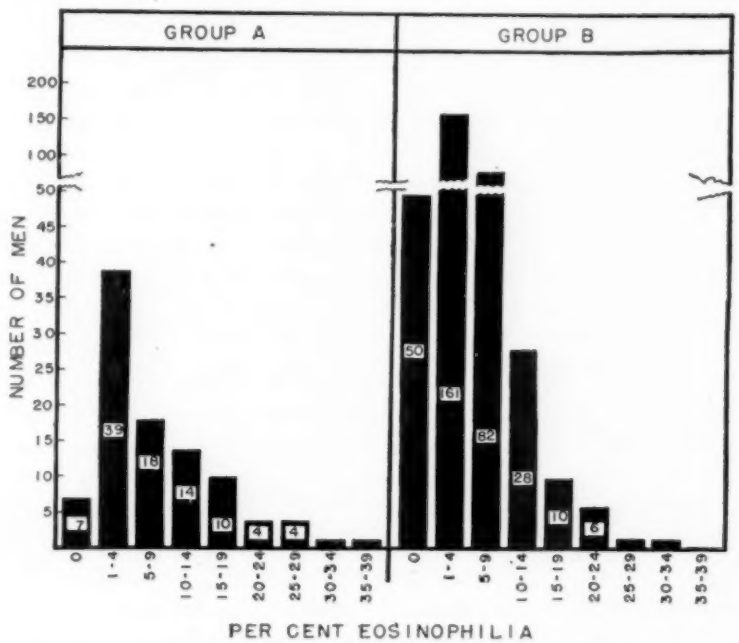

CHART 2. Results of blood smears for eosinophilia on 437 German prisoners of war (not hospitalized). The smears were taken on January 10, 1946 which was six days following the last improperly prepared meal in the prison mess.

Group A (98 men) was the symptomatic group.
Group B (339 men) was the asymptomatic group.

those individuals who during the previous two weeks had noted any of the following symptoms: fever, headache, malaise, muscular pain, or swollen eyelids—the symptomatic group. There were 98 blood smears taken in this group. Group B was composed of those men who felt as well as usual and had had no complaints during the previous two weeks—the asymptomatic group. There were 339 blood smears taken in this group. Twenty-four prisoners were admitted to the hospital between Jan. 10 and Jan. 28, 1946 and thus may have been included in either Group A or B. Of 528 prisoners who were confined to the compound on Jan. 10, 1946 blood smears were taken on 437 men or 82.8 per cent of the entire camp. The remaining 17.2 per cent were not available for study.

A study of the 437 blood smears (Group A and Group B) revealed a high number with eosinophilia present (Chart 2). Conclusions based on one series of differential blood smears, within one week of the last opportunity for infection, could not be considered accurate in determining the total incidence of infection in the compound because of the variable incubation period. However, for this series of blood smears the following arbitrary classification was established: Eosinophilia ranging from 0 to 4 per cent was accepted as within normal limits; eosinophilia ranging from 5 to 9 per cent was considered suggestive of trichinosis under the circumstances prevailing; eosinophilia ranging from 10 per cent to higher levels (36 per cent the highest) was considered as indicating that trichinosis was present. On the basis of this arbitrary classification it was found that 257 individuals or 58.8 per cent had an eosinophilia ranging from 0 to 4 per cent. One hundred (22.9 per cent) had an eosinophilia ranging from 5 to 9 per cent and these individuals were suspected of having trichinosis. Eighty men (18.3 per cent) had an eosinophilia of 10 per cent or greater and they were considered as actually having trichinosis at the time the blood smears were taken. On the basis of these findings it was felt that on Jan. 10, 1946 there were 139 prisoners who actually had trichinosis, 59 of whom had already been hospitalized. It is probable that in addition 100 others were infected (eosinophilia of 5 to 9 per cent). Further studies were not undertaken with this non-hospitalized group.

Summary and Comment

Trichinosis in epidemic proportions was studied in a group of 587 German prisoners of war. Eighty-three were observed in the hospital; 437 who were not hospitalized had blood smears taken (Jan. 10, 1946) approximately one week following the last improperly prepared meal in the prison mess. The presence of eosinophilia in a high percentage of the men not hospitalized suggested the presence of trichinosis in a mild or subclinical form in 100 individuals. On the basis of an eosinophilia of 10 per cent or greater, it was apparent that 80 men actually were infected regardless of the absence of symptoms.

This group of prisoners provided individuals whose activities were closely restricted. All food eaten necessarily came from one source (Quartermaster) and dates of issue of meat as well as amounts issued could be checked. It was known that the prison mess opened on Dec. 4, 1945 and that the first issue of sausage was on Dec. 6, 1945. It was also known that sausage was generally served uncooked. The exact date trichinous meat was served cannot be definitely determined. One patient hospitalized on Dec. 19, 1945 for cellulitis of the hand had initial subjective symptoms of trichinosis on Jan. 1, 1946, along with 19 other men who were not hospitalized at that time. This would suggest that trichinous meat was served on or before Dec. 19, 1945. Another patient, who was transferred into the

compound from a prison camp elsewhere on Dec. 20, 1945, developed initial symptoms of trichinosis on Jan. 15, 1946. It is assumed, therefore, that this man ate infected sausage at one or more meals between Dec. 20, 1945 and Jan. 4, 1946.

The question arises as to whether these men studied were infected prior to their arrival at this installation. It is possible, but with the evidence given and the explosive outbreak of initial symptoms of trichinosis occurring during the first three days of January 1946, it would appear that the source of infection was the uncooked sausage served during December 1945. In 1935 Drake,[2] et. al. reviewed trichinosis epidemics and reported an epidemic that occurred in Maine. It would appear that epidemics generally follow ingestion of improperly cooked sausage from hogs slaughtered on a small scale, and usually involve small groups. Ferenbaugh, et. al.[3] reported an epidemic of 64 cases occurring in a C.C.C. camp in Vermont in 1938. The source of that infection was meat from reliable packers which had had adequate inspection. It is of interest that the epidemic reported here also followed ingestion of meat from reliable packers. The danger of trichinosis is always present when improperly cooked pork is eaten, regardless of the source of the meat.

In this epidemic, which could be considered mild, the typical clinical picture was characterized by a sudden onset of chilliness, fever, malaise, and frontal headache. Associated with these complaints or occurring shortly afterward there was puffiness of the eyelids which generally lasted three to five days. In most instances muscle pain, or muscle pain with tenderness, occurred a few days later. In the typical case clinical muscle pain and tenderness had disappeared or diminished considerably at the time of discharge. Average hospital stay was 26 days. Gastrointestinal complaints, mild in degree, occurred as the initial symptom in less than half of the hospitalized cases.

It was observed that the peak of hospital admissions (17 patients) on Jan. 4, 1946 followed by three days the peak of onset of initial subjective symptoms (20 patients) on Jan. 1, 1946 (chart 1).

The outstanding physical findings were fever (remittent or intermittent in 65 patients) and swollen eyelids. Of the 77 patients who complained of muscle pain, associated tenderness was noted in 48.

The most significant laboratory finding was eosinophilia which ranged as high as 61 per cent. There was no constant relationship between the height of eosinophilia and the leukocyte count. However, at some time during hospitalization 69 patients had leukocytosis greater than 10,000 per cu. mm. Throughout this report the duration of illness has been calculated from the date of onset of initial subjective symptoms. Since it is generally accepted that eosinophilia does not usually appear during the week following ingestion of trichinous meat, it would appear from the high eosinophile counts obtained during the first week (table 2) that the patients were actually

farther along in the course of their disease than indicated. Clinical history, as given by the patient, was almost of equal importance in arriving at a diagnosis. However, this report has shown that patients with significant eosinophilia may have no complaints.

It is probable that many more persons in the group not hospitalized were infected than was evident from a study of their individual blood smears on only one occasion (Jan. 10, 1946).

The small number of muscle biopsies done (10 patients) provided valuable confirmatory information.

Skin tests were of value in diagnosis in 68 patients (84 per cent) of 81 patients in which they were performed.

No complications of trichinosis were observed in this series. No deaths occurred.

Based on studies up to and including Jan. 10, 1946 it is estimated that at least 139 prisoners were infected with trichinosis by that date. The presence of the disease was suspected in an additional 100 prisoners whose eosinophile counts ranged from 5 to 9 per cent on the date mentioned above.

Conclusions

1. Trichinosis may occur in a mild form in epidemic proportions.
2. Trichinosis may occur in individuals without causing subjective complaints.
3. Eosinophilia, swollen eyelids (history or presence of), and positive skin test with trichinella extract are valuable aids in the diagnosis of trichinosis.
4. The height of the eosinophilia in mild trichinosis is not necessarily related to leukocytosis or the severity of the infection.
5. The sedimentation rate in mild trichinosis is usually within normal limits.
6. All pork products, regardless of the source, are potentially dangerous from the standpoint of trichinosis if served improperly cooked.

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PLEUROPULMONARY TULAREMIA: OBSERVATIONS ON 12 CASES TREATED WITH STREPTOMYCIN *

By JOHN S. HUNT, M.D.,† *Nashville, Tennessee*

IN the course of a study of streptomycin therapy of infectious diseases conducted at the Vanderbilt University Hospital and other hospitals in Nashville, the striking results which were obtained in the treatment of tularemia focused attention on this disease. These results were so impressive as to justify the conclusion that streptomycin treatment of tularemia is curative, in the strict sense of the word. The high incidence of tularemic pneumonia and the number of occasions in which the source of the infection was obscure and the diagnosis in doubt, suggested that this form of pneumonia is much more prevalent in this area than is generally recognized. Since tularemic pneumonia is a serious disease with a high mortality rate, its early recognition is a matter of the greatest importance in order that specific treatment may be begun without delay.

The primary pulmonic form of tularemia, as contrasted with pneumonia secondary to bacteremia and localization of *P. tularensis* in the lungs, is probably rare. Although this point is still a matter of debate, clinical evidence suggests that direct infection of the respiratory tract by inhalation of *P. tularensis* may occur, but that it is not a common method of infection. Pneumonia may occur in any of the clinical forms of tularemia. The commonly employed clinical division of tularemia into ulceroglandular, oculoglandular, and typhoidal types is somewhat arbitrary, and tends to fix the attention of the clinician upon the portal of entry of the infection rather than its systemic nature. The incidence of tularemic pneumonia is undoubtedly much greater than is suggested by the number of case reports. Stuart and Pullen [1] in a recent review of the reported cases of tularemic pneumonia in the United States could collect only 253, to which they added 15 of their own. Of these 268 cases, 97 (36.2 per cent) had neither demonstrable primary lesions nor enlargement of superficial lymph nodes and therefore conformed to the so-called typhoidal type of infection. This observation indicates clearly that in a large percentage of cases of tularemic pneumonia, there is no primary tularemic ulcer of the skin or mucous membranes.

The mortality rate of tularemic pneumonia as given by Blackford and Casey [2] in their excellent article on the clinical features of the disease, is in

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† From the Department of Medicine, Vanderbilt University School of Medicine. Clinical Fellow in Medicine of the American College of Physicians.

the neighborhood of 30 per cent. This figure may well be inexact, since the presence of pneumonia may be unrecognized in many mild infections and death may occur in severe infections before agglutinins against *P. tularensis* appear in the patient's serum. Nevertheless, it emphasizes the very serious nature of the infection.

It is now generally recognized that tularemia may be acquired by means other than the handling of tissues of infected wild rabbits and other wild rodents. The list of the known naturally infected vertebrate species in the report of Burroughs et al.[3] is impressive evidence of the large animal reservoir of the infection. The spread of the disease to man through the bites of certain blood sucking ticks and flies has been demonstrated. In the present series, several patients gave histories suggesting the possibility of transmission of the disease by ticks. Since the demonstration by Parker et al.[4] of the wood tick as a possible vector of tularemia, many cases of human infection have been reported in which ticks were suspected or proved as the transmitting agent. The most important tick vectors are apparently the wood tick (*Dermacentor andersoni*) and the common dog tick (*Dermacentor variabilis*).

Streptomycin in the Treatment of Tularemia

P. tularensis has been shown to be highly susceptible to the action of streptomycin in vitro and experimental infections have responded promptly to treatment with the antibiotic.[5] The use of streptomycin in the treatment of human infections was first reported by Foshay and Pasternack.[6] These investigators observed a prompt clinical response in tularemia to the administration of comparatively small doses. Since the publication of this report, the remarkable response of tularemia to streptomycin treatment is rapidly becoming a common clinical experience. Foshay[7] has reported that the results of streptomycin treatment of tularemia as compared with those obtained with the use of hyperimmune serum are roughly comparable and that the therapy-to-recovery interval is not shortened significantly more by one agent than the other. However, he regards streptomycin as the agent of choice in the treatment of patients severely ill with tularemia.

Analysis of Clinical Material

During the period of the study of streptomycin therapy conducted in Nashville hospitals from April to September, 1946, 15 cases of pleuropulmonary tularemia were encountered. Twelve of these patients were treated with streptomycin. Eight of the 12 patients gave no history suggestive of a tularemic ulcer of the skin, and no primary lesions were found on physical examination. In two of the patients (Cases 1 and 3) the presence of pharyngeal ulcers and the occurrence of diarrhea during the early stages of the illness suggested the possibility of infection through the ingestion of infected

meat. Five patients gave a history of contact with wood or dog ticks and it was presumed that their infections were acquired in this manner, although proof of this hypothesis was not obtained. One patient had repeatedly killed and dressed wild rabbits but had no primary tularemic lesion.

Ten of the patients had bronchopneumonia, and in five of these pleural effusions were present. One patient had, in addition, acute pericarditis. There was one instance of tularemic lobar pneumonia. One patient had tularemic pleurisy with a small pleural effusion but no demonstrable pneumonia.

The diagnosis of tularemia was based on a rising serum agglutinin titer against *P. tularensis* and, in certain of the cases, was proved by the intraperitoneal inoculation of mice with sputum or pleural fluid and subsequent culture of the organism from the animals' spleens. Animal inoculation was carried out in 11 of the 12 cases by Dr. G. John Buddingh, Professor of Bacteriology at the Vanderbilt University School of Medicine, with positive results in seven cases. In vitro tests of the susceptibility of the isolated strains to the action of streptomycin were not carried out.

In 11 of the 12 cases streptomycin treatment resulted in dramatic clinical improvement. The one exception (Case 5) was an instance of tularemic bronchopneumonia with cerebral complications. Three patients were semicomatose and desperately ill at the time that they were treated with streptomycin. It is believed that treatment with the antibiotic saved their lives. There was a rise in the serum agglutinin titer in all of the patients during or after treatment with streptomycin. In several cases in which *P. tularensis* had been demonstrated in the sputum or pleural fluid by means of mouse inoculation before the institution of streptomycin therapy, inoculation of additional mice after therapy revealed that the organism had disappeared from these exudates.

One of the patients (Case 7) died suddenly after apparent recovery from tularemic bronchopneumonia. The cause of death appeared to be a massive pulmonary embolism. Permission for postmortem examination was not obtained. Seven of the 11 surviving patients were interviewed and examined at intervals of from one to five months after their discharge from the hospital. All had felt well since leaving the hospital and had resumed normal activity. In only one was there roentgen-ray evidence of residual pulmonary infiltration (Case 3). The original diagnosis in this case was tularemic lobar pneumonia. Roentgen-ray examination five months after the patient's discharge from the hospital revealed the persistence of patchy areas of infiltration in the involved lobe.

The course of the infection and its response to treatment with streptomycin as illustrated by these patients, is presented in tabular form (table 1). Certain of the cases which present features of special interest are reported in detail.

TABLE I

Pleuropulmonary Tularemia

Clinical Features and Response to Treatment with Streptomycin

Case	Patient	Diagnosis	Portal of Infection	Mouse Inoculation Before Treatment	Mouse Inoculation During or After Treatment	Serum Agglutinin Titer at Time of Treatment	Maximum Serum Agglutinin Titer	Maximum W.B.C. (×1000)	Day of Illness on Which Treatment Started	Highest Temperature on Day Treatment Started	Streptomycin Dosage (Intramuscular)	Remarks and Clinical Result
1	W.H.S. 60 yrs. W.M.	Tularemic broncho-pneumonia with pleural effusion	? Oral (pharyngeal ulcers and diarrhea)	+(Sputum) on 14th day of illness	−(Sputum) on 19th day of illness	1:320	1:5,120	10.0	14th	104.2°	0.6 gram daily for six days	Semicomatose at the time treatment was begun. Marked subjective improvement. Cessation of diarrhea. Temperature fell rapidly and was normal after 4 days of treatment. Pleural fluid increased steadily during treatment.
2	L.R. 56 yrs. W.F.	Tularemic broncho-pneumonia with pleural effusion	Ulcer on left hand	+(Pleural) fluid on 14th day of illness	−(Pleural fluid) on 21st day of illness	1:640	1:5,120	10.2	16th	102°	0.6 gram daily for six days	Disappearance of symptoms within 24 hrs. Fall of temperature to normal values within 48 hrs. Slow healing of the primary ulcer and resolution of the pneumonia and pleural effusion over a period of 2 weeks.
3	S.H. 22 yrs. W.M.	Tularemic lobar pneumonia	? Oral (pharyngeal ulcers and diarrhea)	+(Sputum) on 13th and 14th days of illness	Not done	1:2,560	1:1,310,720	16.9	16th	102°	0.5 gram daily for five days	Symptoms disappeared within 24 hrs. Normal temperature after 3 days of treatment. No demonstrable resolution of the pneumonia after 3 weeks. Almost complete resolution after 5 mos. Marked rise in serum agglutinin titer following streptomycin treatment with subsequent fall to lower levels.
4	L.V. 28 yrs. W.M.	Tularemic conjunctivitis, broncho-pneumonia, pleural effusion and pericarditis	Multiple ulcers of left hand	+(Sputum) on 11th day of illness	−(Sputum) on 16th day of illness	0	1:40,960	8.6	11th	102.°4	1.0 gram for one day. 0.5 gram daily for 9 days	Patient semicomatose and desperately ill at the time treatment was started. Mentally clear, with marked subjective improvement, after 12 hrs. of treatment. Temperature fell steadily over a period of 1 wk. Persistent low grade fever during remainder of hospital stay. Rapid disappearance of pericardial friction rub. Slow resolution of the pneumonia and pleural effusion over a period of 2 weeks.
5	J.E. 67 yrs. W.M.	Tularemic broncho-pneumonia ? tularemic encephalitis	Ulcer of left hand	−(Sputum) on 8th day of illness	−(Sputum) on 10th day of illness	0	1:320	12.2	8th	103°	0.8 gram daily for 6 days, 1.6 grams daily for eight days	Slow fall in the temperature to normal values during a period of 5 days with partial resolution of the pneumonia and healing of the primary ulcer. Persistent stupor and headache, and secondary rise of temperature. Increased cell count in the spinal fluid. Apparent clinical response to larger doses of streptomycin.

TABLE I—*Continued*

TABLE I—*Continued*

Case	Patient	Diagnosis	Portal of Infection	Mouse Inoculation Before Treatment	Mouse Inoculation During or After Treatment	Serum Agglutinin Titer at Time of Treatment	Maximum Serum Agglutinin Titer	Maximum W.B.C. (×1000)	Day of Illness on Which Treatment Started	Highest Temperature on Day Treatment Started	Streptomycin Dosage (Intramuscular)	Remarks and Clinical Result
6	C.B. 12 yrs. W.M.	Tularemic broncho-pneumonia ? tularemic encephalitis	Not known (history of skinning wild rabbits)	+(Sputum) on 40th day of illness	Not done	1:2,560	1:5,120	14.8	41st	100°	0.45 gram daily for six days	Patient not acutely ill at the time the treatment was begun and had only slight X-ray evidence of pneumonia. Striking mental confusion and bizarre behavior. Negative spinal fluid. Marked improvement in the mental status occurred after 2 days of treatment. Temperature slowly fell to normal values.
7	W.W. 35 yrs. W.M.	Tularemic broncho-pneumonia	Ulcer of right hand	+(Sputum) on 30th day of illness	Not done	1:640	1:1,280	9.0	31st	104.2°	1.0 gram for one day 0.5 gram daily for seven days	Marked clinical improvement within 24 hrs. after beginning of treatment. Temperature fell to normal after 3 days. Slow resolution of the pneumonia. Sudden death on the 7th day of treatment, apparently from a massive pulmonary embolism. No autopsy.
8	W.C. 23 yrs. W.M.	Tularemic broncho-pneumonia with pleural effusion	Unknown (? tick borne)	Not done	Not done	1:1,280	1:40,960	13.8	18th	103.8°	0.4 gram daily for seven days	Patient critically ill at the time treatment was begun. Definite clinical improvement within 24 hrs. and fall in temperature to normal values over a period of 4 days. Convalescence complicated by femoral thrombophlebitis. Almost complete resolution of pneumonia over a period of 3 weeks.
9	W.M. 30 yrs.	Tularemic broncho-pneumonia	Unknown (? tick borne)	Negative (Sputum) on 9th day of illness	Not done	1:320	1:2,560	13.4	10th	103.6°	1.0 gram for 1 day 0.5 gram daily for six days	Marked clinical improvement and a decline in fever within 24 hrs. Temperature fell to normal values over a 5 day period. Complete resolution of pneumonia after 3 wks.
10	H.H. 37 yrs. W.M.	Tularemic broncho-pneumonia with pleural effusion	Unknown (? tick borne)	+(Sputum) on 4th day of illness +(Pleural fluid) on 13th and 14th days of illness	+(Pleural fluid) on 17th day of illness	1:20	1:2,560	16.6	14th	104.2°	0.8 gram daily for four days 1.6 grams daily for three days	Patient semicomatose and desperately ill at the time treatment was begun. Definite clinical improvement within 24 hrs. Temperature fell steadily to normal levels over a period of one week. Resolution of pneumonia in 2 weeks. Residual pleural thickening.
11	J.C. 58 yrs. W.F.	Tularemic broncho-pneumonia	Unknown (? Tick borne)	−(Sputum) on 12th of illness	Not done	1:320	1:2,560	9.9	13th	102°	0.5 gram daily for six days	Subsidence of symptoms and fall of temperature to normal values within 36 hrs. Almost complete resolution of the pneumonia during a period of 1 week.
12	H.G. 36 yrs. W.M.,	Tularemic pleurisy with pleural effusion	Unknown (? tick borne)	−(Sputum) on 6th day of illness	−(Pleural fluid) on 17th day of illness	0	1:5,120	10.0	14th	102°	0.5 gram daily for seven days	Patient had acute fibrinous pleurisy, and later developed a small pleural effusion. No serum agglutinins after 14 days of illness. Therapeutic trial with streptomycin resulted in a fall in the temperature to normal values. Agglutinins appeared in the serum. Convalescence complicated by the development of thrombophlebitis.

Case 1. (Chart 1) W. H. S. *Tularemic bronchopneumonia with pleural effusion.* This 60 year old white farmer was admitted to the Nashville General Hospital on April 22, 1946, on the service of Dr. R. E. Anderson. Two days before admission he had a severe chill followed by high sustained fever and marked prostration. He became irrational and markedly apathetic. No history of contact with wild rabbits or other rodents could be obtained except that during the week before the onset of illness he had eaten wild squirrels, which had been poorly cooked, on several occasions. He had had no contact with ticks.

On examination he appeared seriously ill. His temperature was 101.6° F. He was irrational and semistuporous. There were no ulcers of the skin and no significant enlargement of the superficial lymph nodes. There were two small, shallow, dirty ulcers on the pharyngeal pillars. Physical signs over the lower lobe of the right lung indicated an area of consolidation, and roentgen-ray examination confirmed the presence of bronchopneumonia. The spleen was not palpable. The leukocyte count was 6,800.

He was treated with penicillin without any effect on his illness. He continued to have high, irregular fever, with daily elevations as high as 105° and became more stuporous. On the fifth hospital day, he began to pass from 15 to 20 watery stools daily. No pathogenic organisms were cultured from the stools. On the eleventh hospital day, roentgen-ray examination of the chest revealed a small right pleural effusion. Serum agglutinins against *P. tularensis,* which had been negative on admission, were now reported positive in dilution of 1:320. A specimen of sputum was injected into mice. These animals died after five days and *P. tularensis* was cultured from scrapings of their spleens. Stool suspensions were rubbed into the shaved abdominal skin of other mice but no tularemic ulcers developed. Streptomycin (0.6 gram daily, given in divided doses intramuscularly at four hour intervals) was begun on the twelfth hospital day and the fourteenth day of illness. Within 24 hours he was markedly improved and was rational and alert. The diarrhea ceased. The temperature fell abruptly to lower values and within four days had become normal. Streptomycin treatment was continued for two additional days. The pleural effusion increased steadily in amount during treatment, but animal inoculation with both sputum and pleural fluid on the nineteenth day of the illness was negative. The pharyngeal ulcers healed slowly. The serum agglutinin titer rose to 1:5120. On the last day of streptomycin therapy, right thoracentesis was performed to relieve slight respiratory embarrassment and 1,000 c.c. of serosanguineous fluid were removed. Mice were inoculated with this fluid with negative results. At the time of discharge, the patient felt well although a roentgenogram revealed the persistence of a small amount of fluid in the right pleural cavity.

Comment: In this patient the presence of pharyngeal ulcers and the occurrence of severe diarrhea during the early stages of his illness suggested the possibility of an oral portal of infection. The diagnosis of tularemia was suspected but was not confirmed by serum agglutination tests until the eleventh day of illness, at a time when the patient was critically ill. Streptomycin treatment resulted in prompt clinical improvement. The marked subjective improvement and the abrupt cessation of diarrhea before the temperature had fallen to normal values were striking.

Case 4. (Chart 2) L. V. *Tularemic conjunctivitis, pneumonia, pleural effusion, and pericarditis.* A 28 year old white farmer was admitted to the Vanderbilt University Hospital on May 29, 1946. About two weeks before admission he had skinned a wild rabbit and had cut his hand. Ten days before admission multiple ulcers ap-

peared on his left hand and at approximately the same time he developed high fever and severe headache and malaise. Three days later he developed a cough which was productive of yellow sputum.

At the time of admission to the hospital he was critically ill. His temperature was 102.6° F. He was semicomatose and delirious. He coughed frequently, producing moderate amounts of tenacious yellow sputum. There was moderate dyspnea but cyanosis was not striking. There was a purulent left conjunctivitis. On the fingers of the left hand were three small shallow ulcers with indurated black margins. The left epitrochlear lymph node was enlarged and tender and there were subcutaneous nodules along the medial aspect of the left forearm. The left posterior cervical lymph nodes were moderately enlarged and tender. There were physical signs of a large left pleural effusion. A loud pericardial friction rub was audible. The spleen was felt at the costal margin. The leukocyte count was 4,600. Roentgen-ray examination of the chest confirmed the presence of a large left pleural effusion.

Before the administration of streptomycin a specimen of sputum was injected into mice. These animals died after five days and *P. tularensis* was cultured from scrapings of their spleens. No agglutinins against *P. tularensis* were demonstrated in the patient's serum. One gram of streptomycin was given intramuscularly during the first 24 hours. Thereafter, 0.5 gram was given daily. Twelve hours after the beginning of this treatment there was marked clinical improvement, although the temperature remained at high levels. He became rational and alert and dyspnea diminished. Within 48 hours the temperature had declined markedly and there was striking improvement in the appearance of the local lesions. The conjunctivitis had entirely cleared and the left epitrochlear and cervical nodes were smaller and less tender. He coughed less frequently and the sputum became mucoid. The pericardial friction rub disappeared, and no pericardial effusion developed. On the fourth hospital day, left thoracentesis was performed and 1,250 c.c. of serosanguineous fluid were removed. Specimens of the pleural fluid and of sputum obtained on the same day were injected intraperitoneally into mice but the animals survived. Following the removal of the pleural fluid there were physical signs over the left lower lobe indicating areas of consolidation, but upon subsequent roentgen-ray examination of the chest the residual pleural fluid obscured the lung fields. Streptomycin treatment was continued for a total of 11 days because of the persistence of low grade fever. There was progressive healing of the ulcers of the hand and decrease in the size of the lymph nodes. Physical and roentgen-ray examination of the chest revealed a decrease in the pleural effusion, although at the time of discharge on June 20 there was still a moderate amount of fluid in the left pleural cavity. The serum agglutinin titer rose steadily to 1:40,960. On examination two months later he was found to have some residual pleural thickening but no pleural fluid. He felt well and was at work on his farm. The serum agglutinin titer was 1:20,480.

Comment: The diagnosis in this case was obvious, although it is of interest that there were no serum agglutinins against *P. tularensis* on admission after 11 days of illness. The serum agglutinin titer rose rapidly and to high levels after streptomycin treatment. The response to streptomycin treatment was striking.

Case 5. (Chart 3) J. E. *Tularemic bronchopneumonia (?), tularemic encephalitis.* This 67 year old white farmer was admitted to the St. Thomas Hospital on July 7, 1946 on the service of Dr. B. H. Webster. Two weeks before admission, he had skinned a wild rabbit which had been caught by his dog. Five days before admission an ulcer appeared on his left thumb, and he had a shaking chill. He developed a severe headache and the following day had pleuritic pain in his right chest

and a non-productive cough. High fever and intense headache continued, and he became markedly prostrated.

The temperature at the time of his admission to the hospital was 102°. He was semistuporous but responded to questions and complained of severe headache. There was an indurated ulcer on the left thumb. The left epitrochlear and axillary lymph nodes were enlarged and tender. There were many fine moist râles over both lung fields, and a roentgenogram of the chest revealed diffuse bilateral bronchopneumonia. The leukocyte count was 10,600.

During the next few days he ran a high irregular fever and appeared acutely ill. His stupor deepened, and he became incontinent of urine and feces. A bilaterally positive Babinski sign appeared. Treatment with penicillin was ineffective. No agglutinins against *P. tularensis* were demonstrated in the serum. A specimen of sputum was injected intraperitoneally into mice, but the animals survived. Streptomycin treatment was begun on the third hospital day in doses of 0.8 gram daily, given intramuscularly in divided doses at four hour intervals. The temperature fell to normal over a period of five days, and definite clearing of the pneumonia was demonstrated by roentgen-ray examination. The ulcer of the left thumb began to heal. However, the patient continued to be stuporous and his temperature again rose, reaching a level of 102.4°. A lumbar puncture on the ninth hospital day yielded clear spinal fluid under normal pressure. The fluid contained 29 leukocytes per cu. mm., the majority of which were granulocytes. The protein content was 20 mg. per 100 c.c. Since the possibility existed that the cerebral process was tularemic, the dose of streptomycin was doubled. Within 48 hours after the dose of streptomycin had been increased, the patient showed marked clinical improvement. He was mentally alert and was free of headache. Serum agglutinins against *P. tularensis* were demonstrated for the first time on the fifteenth day of illness, in titer of 1:40. Streptomycin was continued for an additional week, a total of two weeks treatment. There was a gradual fall in the temperature to normal values. The Babinski signs disappeared. The serum agglutinin titer rose to 1:320. On the eighteenth hospital day the lumbar puncture was repeated. The fluid contained 2 leukocytes per cu. mm., and its protein content was 60 mg. per 100 c.c. The patient was discharged on the twenty-first hospital day, afebrile and clinically well.

When seen six weeks later, he felt well. There were no physical signs of pulmonary consolidation. The serum agglutinin titer was 1:320.

Comment: This case is presented in detail since the response to streptomycin was by no means as striking as that observed in the other patients. The diagnosis of tularemic pneumonia was not proved by the demonstration of the organism in the sputum. However, the appearance of serum agglutinins against *P. tularensis* after treatment with streptomycin supported the clinical diagnosis. The rise in agglutinin titer was not as rapid nor as marked as that observed in the majority of the patients in this series after streptomycin treatment. It is of interest that agglutinins were not demonstrated until the dose of streptomycin had been increased. The nature of the cerebral complication was not clear. The clinical picture and the improvement following larger doses of streptomycin suggest that tularemic lesions may have been present in the brain.

Case 10. (Chart 4) H. H. ***Tularemic bronchopneumonia with pleural effusion.*** A 37 year old white business man was admitted to the Vanderbilt University Hospital on July 21, 1946, on the service of Dr. Robert M. Finks. Ten days before admission

he developed high fever and pleuritic pain in the right chest. Physical examination of the chest was negative, but he was treated by his physician with sulfathiazole on the assumption that he had pneumonia. He continued to have high fever and became progressively worse. He developed a cough productive of moderate amounts of mucopurulent sputum. Sulfathiazole was discontinued, and penicillin and sulfadiazine were administered without any effect on the illness. On the sixth day of his illness fine râles and a friction rub were heard over the base of the right lung. During the next few days he became dyspneic and moderately cyanotic. Because of the failure of his pneumonia to respond to treatment with penicillin and sulfadiazine, he was referred to the hospital. He gave no history of contact with wild rodents. He lived in suburban Nashville in a region rather heavily infested with ticks and had removed wood ticks from dogs on numerous occasions. He had worn rubber gloves and recalled no tick bites.

On physical examination at the time of admission he appeared acutely ill. His temperature was 103.2° F. He was dyspneic, cyanotic, and mentally confused. There were no skin lesions and no enlargement of the superficial lymph nodes. The percussion note over the right chest was dull below the level of the sixth rib. Tactile and vocal fremitus were diminished in this area, and the breath sounds were suppressed and bronchovesicular in character. Many fine moist râles were audible over the area of dullness. The spleen was not palpable. The leukocyte count was 16,000. A roentgenogram of the chest revealed an area of consolidation in the right hilar region and a moderate amount of fluid in the right pleural cavity.

Under observation in the hospital irregular fever continued with daily rises as high as 104.2° F. The patient's condition became progressively worse in spite of treatment with penicillin and sulfadiazine. On the third hospital day right thoracentesis yielded 60 c.c. of grossly bloody fluid. The fluid contained 12,000 leukocytes per cu. mm. and cultures were sterile. He became more stuporous and on the following day was semicomatose and appeared desperately ill. A serum agglutinin titer against *P. tularensis* of 1:20 was reported. A second right thoracentesis yielded 450 c.c. of dark, bloody pleural fluid. A therapeutic trial with streptomycin was decided upon. Before the administration of streptomycin a specimen of sputum was obtained, and this, together with the specimens of pleural fluid, was injected intraperitoneally into mice. All of the mice subsequently died, and *P. tularensis* was cultured from their spleens. Streptomycin treatment was begun in doses of 0.8 gram daily given intramuscularly in divided doses at four hour intervals. The following day the temperature was somewhat lower, and the patient's mental state was clearer. On the second day of treatment the temperature had fallen to even lower levels. He was mentally alert, and there was marked decrease in the dyspnea and cyanosis. Right thoracentesis was performed on the fourth day of treatment and 450 c.c. of bloody fluid were removed. This fluid was injected into mice. The mice died after four days, and *P. tularensis* was again cultured from the splenic scrapings. Although this result was not immediately available to the clinician, the dose of streptomycin was doubled after three days of treatment because the patient's response was not as dramatic as had been anticipated. Progressive improvement continued, and the temperature fell steadily to normal levels. Treatment was continued for a total of seven days. Right thoracentesis on the fifth and nineteenth days of illness yielded 410 c.c. of blood-tinged fluid, but on the twenty-second day of illness only 15 c.c. of fluid could be obtained. Animals inoculated with these specimens survived. Roentgen-ray examination of the chest showed considerable clearing of the right lung field but some pleural thickening. The serum agglutinin titer rose progressively to 1:2,560. The patient was discharged on the eighteenth hospital day. When seen one month later he felt well. Fluoroscopic examination of the chest showed residual pleural thickening. The serum agglutinin titer was 1:1,280.

Comment: This patient had no primary tularemic lesion. The history of contact with dog ticks suggested that he might have acquired his infection in this manner. He was critically ill at the time treatment with streptomycin was instituted and it is believed that it saved his life. The diagnosis of tularemic pneumonia had not been confirmed definitely by laboratory studies, and streptomycin administration was in the nature of a therapeutic trial. The dose of streptomycin was increased in an effort to determine whether larger amounts of the antibiotic would result in a more striking clinical response. This seemed to be the case. The smaller doses may well have effected cure of the infection, but in this connection it is noteworthy that *P. tularensis* was recovered from the pleural field on the fourth day of treatment with these doses. The rapid rise in the serum agglutinin titer against *P. tularensis* after the institution of streptomycin treatment has been observed in the majority of the patients in the present series.

Case 12. (Chart 5) H. G. *Acute tularemic pleurisy.* This 36 year old white farmer and woodcutter was admitted to the Vanderbilt University Hospital on August 18, 1946. His illness began suddenly two days before admission with a shaking chill, followed by high fever and sharp epigastric pain. The pain was quite severe for about an hour and then subsided, leaving him with a continuous dull ache in the same area. Coughing, moving or straining caused marked discomfort. He gave no history of any contact with wild rodents, but during his work as a woodcutter he had repeatedly removed wood ticks from his skin. The ticks had not embedded themselves and he had noticed no ulcers.

On physical examination he appeared acutely ill. His temperature was 102° F. There were no ulcers of the skin or mucous membranes. The superficial lymph nodes were not enlarged. The lungs were clear to auscultation. There were marked tenderness and voluntary spasm of the upper abdomen bilaterally. The spleen was felt one finger's breadth below the costal margin. The leukocyte count was 6,100.

The patient ran a high irregular fever during his first week in the hospital. His epigastric pain and tenderness subsided within 24 hours, but on the day after admission he developed pleuritic pain in the left chest and a pleural friction rub was audible. A roentgen-ray of the chest revealed clear lung fields. On the fifth hospital day there were physical signs suggesting the presence of a left pleural effusion, and the patient raised small amounts of mucopurulent sputum. Mice were inoculated intraperitoneally with sputum, with negative results. Another roentgenogram of the chest revealed no evidence of a pleural effusion. Left thoracentesis was performed, but no fluid could be obtained. A third roentgenogram of the chest on the ninth hospital day showed a small pneumothorax, presumably resulting from the previous thoracentesis, but no pleural fluid. The patient was now free of pleural pain, his temperature had fallen to somewhat lower values, and he had no complaints except for moderate malaise and weakness. No serum agglutinins against *P. tularensis* were demonstrable on the third, seventh, and twelfth hospital days. On the twelfth hospital day, and the fourteenth day of illness, streptomycin treatment was begun as a therapeutic trial. Streptomycin was administered in doses of 0.5 gram daily in divided doses at four hour intervals. Within 24 hours his malaise had disappeared and he said that he felt perfectly well. The temperature slowly fell to normal levels over a period of four days. On the fifteenth hospital day, fluoroscopy of the chest revealed a small left pleural effusion. Left thoracentesis was done the following day and 8 c.c. of straw colored fluid were removed and injected into mice. The mice survived. On the following day, the seventeenth day of illness, agglutinins against *P. tularensis* were demonstrated in the serum for the first time, in a titer of 1:160. During the next week

there was a progressive rise in the serum agglutinin titer to 1:640. The pleural effusion gradually disappeared. Convalescence was complicated by the development of a left femoral thrombophlebitis associated with low grade fever and considerable swelling of the leg. Recovery was complete after a period of eight days. He was discharged on the thirty-first hospital day. At this time the serum agglutinin titer had risen to 1:5,120.

Comment: The diagnosis of tularemic pleurisy, without detectable pneumonia and with only a small pleural effusion, seems to have been established in this patient. He was treated with streptomycin solely as a therapeutic trial since laboratory confirmation of the diagnosis had not been obtained. The patient was not seriously ill at the time that treatment was instituted but exhibited a convincing clinical response to streptomycin.

Discussion

Observations on the Response of Tularemic Pneumonia to Treatment with Streptomycin

Certain features in the response of these patients to streptomycin treatment seem worthy of comment.

Subsidence of Symptoms Following Treatment. In all of the patients obvious clinical improvement and subsidence of the constitutional symptoms —headache, aching in the extremities, mental lethargy or stupor, and prostration—occurred before the fall of temperature to normal values.

Temperature Response. In the patients with high fever at the time treatment was begun, the temperature usually declined within 24 hours, but in many instances it did not reach normal values until several days had elapsed.

Disappearance of P. tularensis, *from Exudates.* The results of animal inoculation of sputum or pleural fluid seemed to support the clinical impression that streptomycin treatment resulted in a rapid elimination of *P. tularensis* from the lesions of the lungs and pleura. In several instances, in which the organism had been demonstrated in sputum or pleural fluid by mouse inoculation prior to the institution of streptomycin treatment, additional mice were inoculated in an attempt to demonstrate the rapidity with which it was eliminated from these exudates and, by inference, from the tissues. The organism was recovered in only one instance after the institution of streptomycin treatment (Case 10). This patient was critically ill at the time that he was treated with streptomycin and *P. tularensis* was recovered from the pleural fluid on the fourth day of treatment. Animal inoculation of specimens of pleural fluid obtained subsequently was negative.

Regression of Lesions. In contrast to the marked clinical improvement which was observed, there was comparatively slow resolution of the pulmonary consolidations and pleural effusions, reduction in the size of the regional lymph nodes, and healing of the primary tularemic ulcers. The resolution and healing of these lesions were felt to have been accelerated somewhat by streptomycin treatment, although complete healing usually was not evident for several weeks.

Effect of Streptomycin on the Immune Response. The effect of streptomycin treatment on the immune response of the patient with tularemia is a subject of considerable interest. It was considered possible that early treatment with the antibiotic might prevent the development of acquired immunity and expose the individual to the danger of reinfection. None of the patients in the present series was treated within the first week of illness. However, in all of them, even those who had no demonstrable serum agglutinin or agglutinins in low titer at the time of treatment, a rise in titer occurred following streptomycin therapy. In several patients this rise was pronounced and rapid, suggesting that the destruction of large numbers of organisms had provided a marked antigenic stimulus. It is not known at present whether streptomycin treatment of tularemia will have any effect on the length of persistence of serum agglutinins. In six of the seven patients who were studied after an interval of several months, the serum agglutinin titer was either unchanged or only slightly lower than at the time of discharge from the hospital. One patient (Case 3) whose serum agglutinin titer rose to the remarkable level of 1 : 1,310,720 had a titer of only 1 : 1,280 five months after discharge from the hospital.

Dosage. Comparatively small doses of streptomycin were employed. Since the first patients in the series were treated with as little as 0.5 gram of streptomycin daily and showed a favorable clinical response, subsequent patients were given comparable doses. No instance of relapse of the infection was observed. These doses are smaller than those recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council in its recent report on the use of streptomycin in the treatment of infectious diseases.[8] The use of larger doses of the antibiotic in the treatment of severe infections is probably advisable. The evidence presented in this report indicates that the small doses of streptomycin which were employed cured the infection. However, larger doses of the antibiotic might conceivably have produced a more rapid response. In addition, the possibility of the acquisition of resistance by *P. tularensis* to the action of streptomycin exists, although no instance of this development has been reported. In all of the patients in the present series, streptomycin was injected intramuscularly in divided doses at four hour intervals. Streptomycin was not injected intrapleurally in patients with pleural effusions.

The Frequency of Tularemic Pneumonia and the Importance of Early Diagnosis and Treatment

Study of this group of patients suggests that the frequency of tularemic pneumonia and pleurisy in central Tennessee, an area in which the tularemia is endemic, is probably much greater than is generally recognized. Since the incidence of human infections may be, in part, a reflection of the prevalence of the infection in the animal reservoir, it is possible that the apparent high incidence of severe tularemia with pneumonia may have resulted from an unusually high infection rate among native wild rodents. This

possibility was not investigated by field studies. Similarly, the number of cases in which tick transmission of the disease was a possibility may have been influenced by the season of the year in which the study was carried out. Even with these reservations, it would appear that tularemic pneumonia is by no means uncommon in this area and that it is unrecognized in many instances. This statement may also apply to other endemic areas in the United States. In three patients in this series a clinical diagnosis of severe atypical pneumonia, probably of viral origin, had been made at the time of their admission to the hospital. Our experience strongly indicates that at least one factor favoring recognition of tularemic pneumonia is the stimulus provided by the availability of a specific therapeutic agent.

The difficulties inherent in the laboratory confirmation of the diagnosis of tularemia were apparent in this study. It is important to recognize that during the early stages of the infection current methods may be of little value. The macroscopic serum agglutination test is usually relied upon for verification of clinical diagnosis. Although this test is extremely reliable, it is never positive during the first week of illness and, occasionally, agglutinins may not appear in the serum until the third or, rarely, the fourth week of illness.[9] This test is therefore unsatisfactory as an early diagnostic procedure. Isolation of *P. tularensis* from exudates by means of animal inoculation is hazardous for laboratory workers. Moreover, from four to seven days usually elapse before the animal dies and the infecting organism can be identified by stained smears or cultures. The intradermal test of Foshay,[10] in which a killed bacterial suspension is used as the test solution, is said to be highly specific. Intradermal tests were not employed in this study and their value in early diagnosis cannot be assessed.

Since the clinical diagnosis of tularemic pneumonia is frequently difficult and the commonly employed laboratory methods are not of great value in the early stages of the illness, a therapeutic test with streptomycin is a valuable diagnostic aid and has the great advantage of instituting specific treatment for the infection, which is usually severe and often lethal, without unnecessary delay. The rise in the serum agglutinin titer against *P. tularensis* which occurs during or after streptomycin treatment provides further confirmation of the diagnosis. Streptomycin was administered to two patients in this series as a therapeutic test. In one patient (Case 10), the serum agglutinin titer at the time of treatment was 1:20, and in the other patient (Case 12) there were no agglutinins in the serum after two weeks of illness. Both of these patients responded promptly and in one of them (Case 10) streptomycin was judged to have been lifesaving. In this case, *P. tularensis* was subsequently isolated from mice injected with sputum and pleural fluid before the institution of treatment. On the basis of the clinical data presented here, the administration of 1 to 2 grams of streptomycin daily for two days is suggested as an adequate therapeutic test. If clinical improvement occurs the antibiotic should be administered for a longer period.

Summary and Conclusions

Streptomycin was used in the treatment of 11 cases of tularemic pneumonia and one case of tularemic pleurisy. The patients showed a prompt clinical response to small doses of the antibiotic. The rapid disappearance of *P. tularensis* from the sputum or pleural fluid, as determined by animal inoculation, indicated that the organism was rapidly killed in the tissues. The regression of pulmonic lesions and the healing of primary ulcers were believed to have been accelerated by streptomycin treatment but required a longer time interval than did clinical recovery. In all of the patients a rise in serum agglutinin titer occurred after treatment and in certain instances was very marked and rapid. This increase in the serum agglutinin level may have resulted from the antigenic stimulus provided by the destruction of large numbers of organisms.

The incidence of tularemic pneumonia during the period of study was striking. Because of the diagnostic difficulties presented by many cases of tularemic pneumonia and the prompt response of tularemia to streptomycin therapy, the value of a therapeutic trial with this antibiotic in severe pneumonia of undetermined origin in areas in which tularemia is endemic is apparent. In those cases which are due to *P. tularensis* withholding streptomycin in order to confirm the diagnosis by laboratory methods may, on occasion, endanger life. A dosage of 1 or 2 grams daily for two days is suggested as an adequate therapeutic trial in such patients.

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CASE REPORTS

STEVENS–JOHNSON SYNDROME, A VARIATION OF ERYTHEMA MULTIFORME EXSUDATIVUM (HEBRA): A REPORT OF TWO CASES *

By Henry S. Wentz, M.D., and Harvey H. Seiple, M.D., F.A.C.P.,
Lancaster, Pennsylvania

Two cases are presented—the first a syndrome of ulceromembranous stomatitis, purulent conjunctivitis, urethritis, and signs of constitutional toxicity; the second an eruptive bullous type febrile disease associated with stomatitis and ophthalmia. Both cases conform to the picture described by Stevens and Johnson. Stevens and Johnson [3] in 1922 felt that their syndrome of an eruptive febrile disease associated with stomatitis and purulent conjunctivitis was a distinct clinical entity. Controversy exists, however, as to whether the syndrome should be differentiated from erythema multiforme exsudativum.

Fletcher and Harris [1] in 1945 and Keil [2] in 1940 have presented excellent historical reviews. Erythemas were first described in 1808 by Willan and Bateman; Alibert and Bazin were the first to note an erythema-like skin rash in association with conjunctivitis and stomatitis in 1822; membranous conjunctivitis with skin rash was described in 1855; in 1866 von Hebra described *erythema exsudativum multiforme;* French investigators in 1917 described necrotic pseudomembranous excoriating mucous membrane lesions involving the mouth, eyes, genitalia, vagina and rectum either without or with multiform erythematous skin lesions.

The two cases presented were admitted 18 days apart. They were similar, except for the fact that the one did not have an erythema multiforme-like skin rash. It seems likely that all such cases belong in the *erythema multiforme exsudativum* group which has been described so well by Fletcher and Harris,[1] and Keil,[2] and further defined by Koke.[4]

Case Reports

Case 1. D. Y., 37 year old white male, was referred to the Lancaster General Hospital on November 21, 1945, as a case of an unexplained oral mucous membrane lesion of two days' duration. Four days before admission he developed extreme malaise and drowsiness, aches and pains in his joints and back, fever and profuse night sweats, and cough with slight expectoration. Two days before admission he developed blisters under the upper lip followed by sore throat with difficulty in eating and swallowing. Excessive lacrimation had been present for two days. Burning on urination had been present for one day.

The family history was non-contributory. The general health had been good except that two years previously blisters had appeared in his mouth on one occasion but this was of short duration.

On physical examination the temperature was 103.2° F., pulse 100 per minute, and respirations 20 per minute. The patient appeared acutely ill, but oriented and co-

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operative. The skin was dry and no eruption was present. The conjunctivae were markedly hyperemic, and a purulent exudate was present. The ear drums and canals were normal and there was no nasal obstruction. The lips were swollen and ulcerated and the mucous membranes of the palate and gums were ulcerated, the ulcers being covered by a confluent membranous exudate; the tongue was swollen and covered by a membranous exudate; a foul odor was present. The nasopharynx was reddened and a few small ulcers were present. The submaxillary lymph nodes were enlarged bilaterally. Examination of the chest revealed increased bronchovesicular sounds in the left hilar area and a few musical râles throughout the chest. The examination of the heart was negative. Blood pressure was 130 mm. Hg systolic and 70 mm. Hg diastolic. The abdomen and extremities were normal. Reflexes were normal.

Laboratory findings were as follows:

Date	Hgb.	W.B.C.	Polys.	Lympha.	Monos.	Eos.
11/21/45	92%	23,800	93%	7%	—	—
11/24/45	92%	8,900	65%	33%	1%	1%
11/27/45	79%	10,800	60%	39%	1%	—
11/30/45	—	15,000	—	—	—	—
12/ 7/45	79%	10,500	69%	27%	2%	2%

Urinalyses revealed a 1 plus albumin on two occasions and on November 22, 1945 there were a moderate number of finely and coarsely granular casts and a few hyaline casts present. On November 25, 1945 there was a 1 plus albumin but no casts were present. The Wassermann test was negative. Blood cultures on the second hospital day and the twelfth hospital day were negative. Smears from the mouth showed the following: gram positive cocci in pairs and chains, large and small gram negative rods (*N. catarrhalis*), no fusospirochetal organisms, and no *C. diphtheriae*. Cultures from the mouth showed hemolytic streptococci, *N. catarrhalis*, pneumococcus; negative for fungi. An anaerobic culture showed gram positive cocci in chains. Eye smears and cultures revealed *Staphylococcus albus*, diphtheroid bacilli, and *N. catarrhalis*. Smear and culture from the membrane over the urethra showed *Staphylococcus albus;* the pathological report was "fibrinopurulent membrane." Heterophile antibody test was positive in dilutions of 1:28. The Widal and the brucella agglutination tests were negative. Prothrombin time was 17 seconds. Platelet count was 599,400. Bleeding time was one minute and the coagulation rate was six minutes.

Roentgenogram of the chest on November 23, 1945 showed some infiltration in the left base and the right cardiohepatic angle, due to some stage of bronchopneumonia. Hilar shadows on the left side were exaggerated and contained one to two moderate sized glands. On December 3, 1945 a roentgenogram of the chest showed decrease in the pneumonic infiltration in both lungs with improvement especially apparent in the left. There was slight infiltration about the lower bronchi on both sides. Glandular enlargement in the hilus was not so pronounced.

Two days after admission there was some decrease in the inflammation of the mucous membrane lesion of the mouth and pharynx. There was increased cervical gland involvement and a violent ophthalmia was present. Three days after admission the patient complained of burning on urination and later of an inability to void; a tenacious membrane was removed from the urethral orifice and voiding occurred. This recurred two days later. His status on the fourth day after admission was (1) generalized toxicity, (2) ulcerative membranous stomatitis, (3) purulent ophthalmia, (4) membranous lesion over mouth of urethra, (5) albuminuria and casts, (6) bronchopneumonia, (7) nose bleeding, and (8) polymorphonuclear leukocytosis.

Constant improvement occurred from the seventh hospital day on. The membrane sloughed from the mucous membrane of the mouth leaving a raw ulcerated

surface. He was discharged on the twentieth hospital day with mild injection of the conjunctivae and with a small amount of membrane remaining on the soft palate.

He received 2,000 c.c. of 5 per cent glucose in normal saline intravenously on the day of admission. Penicillin, 20,000 units every three hours intramuscularly, was administered from the day of admission until the seventeenth hospital day. Ascorbic acid 100 mg. twice daily, and nicotinic acid 100 mg. twice daily by mouth; and Bejectal, 2 c.c., twice daily hypodermically, were administered during the hospital stay. Zinc sulfathiazole ointment, 5 per cent, was applied three times daily to the eyes. Penicillin paste was applied to the mouth and gums three times daily. Sodium perborate and diluted hydrogen peroxide mouth washes were used locally.

One month after discharge he complained of a burning sensation of the eyes at times, numbness at the end of the tongue, impairment of taste, abdominal pains between meals, and a burning feeling on defecation. A mild conjunctivitis was present but physical examination was otherwise normal. A barium enema was negative.

Case 2. A boy, age 11, entered the Lancaster General Hospital on December 7, 1945, complaining of sore mouth, sore eyes, and a rash on the hands and feet. Five days before admission his eyes had become inflamed. They watered considerably, and he complained that light hurt them. The day before admission the mouth and lips became sore. The same day a vesicular rash was noticed on one foot. On the day of admission the hands and feet were covered with this eruption as well as some spots on the arms and legs. A cough had been present for two days.

The family history was non-contributory except for diabetes in the maternal grandmother. The patient had had chickenpox, mumps, measles, tonsillectomy and adenoidectomy in childhood. At the age of five he had shown a faint trace of sugar in the urine, at which time he was put on a diet restricting starches and sweets for a year. There was no history of allergy to foods or pollens.

On physical examination the patient was acutely ill with a temperature of 103° F., pulse rate 120 per minute, and respiratory rate 28 per minute on the day of admission. Red vesicles and bullae were scattered over the face, hands, feet, and a few over the body. Smaller skin blebs resembled those of chickenpox. There was a good vaccination scar on the left arm. Eye examination showed a marked swelling of the lids with a serous discharge which had caked in slight yellowish crusts in the lashes. The conjunctivae were congested but showed no lesions similar to those in the mouth. There was congestion of the nasal mucous membranes. The ears were normal. The lips were covered with a grayish necrotic crust which covered ulcerated areas. Similar lesions involved the mucous membrane of the entire mouth, gums, and tongue. The pharynx was red and inflamed. There was bilateral cervical adenopathy most pronounced on the left side. Numerous coarse râles were heard anteriorly and posteriorly over the entire chest. The heart was normal. The abdomen was normal. The extremities were normal except for the skin lesions.

Laboratory findings were:

Date	Hgb.	R.B.C.	W.B.C.	Polys.	Lymphs.	Monos.	Eos.
12/ 9/45	79%	4,160,000	9,100	75%	22%	1%	2%
12/18/45	79%	3,930,000	9,800	58%	42%		

Several urinalyses were normal. Sedimentation rate on Dec. 18, 1945 was 17 mm. in one hour (Westergren). Smears from the eyes showed no definite organism; subculture from the eyes showed hemolytic *Staphylococcus aureus* and *Staphylococcus albus* on Dec. 10, 1945. Subculture from the mouth showed streptococcus and *Staphylococcus aureus,* the mixed growth of which was markedly hemolytic. On Dec. 18, 1945 smears from the mouth showed gram positive diplococci and gram

negative diplococci and many small gram negative bacilli. The smears were negative for Vincent's organisms. Broth culture from the mouth showed gram positive cocci in chains. Broth culture from the eyes showed gram positive cocci in chains and clusters. Blood culture was negative. The Widal and brucella agglutination tests were negative in dilutions 1:40 and 1:80. A roentgenogram of the chest on Dec. 10, 1945 showed a haziness in both upper lobes which appeared to be due to a peribronchial thickening. The right side showed the findings of early bronchopneumonia. There were enlarged glands in both hilar areas. Roentgen examination of the chest on

FIG. 1. Photograph of patient presented as case 2 on fifth day of hospitalization.

Dec. 24, 1945 showed a decided improvement in the appearance of the lung fields due to resolution of the bronchopneumonia. There were still several enlarged glands in the hilar areas.

Fever and increased pulse rate continued for 11 days after admission. On Dec. 9, 1945 there was considerable difficulty in swallowing. On Dec. 10, 1945 some of the bullae had entered the state of flattened skin lesions three-quarters inch to one inch in circumference. The lesions of the lips and eyes had become pustular. The

edema of the membrane of the mouth and palate was slightly less marked and liquids could be swallowed more easily. Skin and mouth lesions gradually improved. As the necrotic material in the mouth was removed the bright red ulcerations presented themselves. The skin of the feet became denuded. On Dec. 16, 1945 there was still considerable cervical gland enlargement. Areas of the mouth were denuded of membrane with areas of red tissue presenting. On Dec. 24, 1945 several finger nails and toe nails showed evidence of adjacent infection, and eventually all the nails sloughed off and new nails appeared.

Treatment consisted of boric acid solution, ophthalmic penicillin ointment to the eyes, a hydrogen peroxide mouth wash, supplemental vitamin therapy, penicillin 20,000 units intramuscularly every three hours from Dec. 8, 1945 to Dec. 16, 1945 and penicillin 15,000 units intramuscularly every three hours from Dec. 16, 1945 to Dec. 19, 1945. The patient was discharged on Dec. 24, 1945.

The following cases are listed:

Author	Year of Disease	Age	Sex	Duration	Complications	Remarks
Stevens and Johnson [3]	1922	8	M		Corneal scar	
Stevens and Johnson [3]	1922	7	M		Total loss vision	
Wheeler [5]	1927	8	M	About 3 months	Loss sight	
Bailey [6]	1927	39	M	6 weeks	Nails of all digits fell off; 3 years afterward blind due to corneal opacification	
Bailey [6]	1927	9	M	1 month	Poor vision; in institution of home for blind	
Bailey [6]	1927	7	M	18 days	Blind except for perception of light	
Rutherford [7]	1928		M	27 months	Removal both eyes	
Ginandes [8]	1931	5½	M	8 weeks		
Edgar and Syverton [9]	1933	12	M	Temperature normal in 9 days; recurrence 6 mos. later—well in 6 days; recurrence 2 years later		
Fletcher and Harris [1]	1932	16	M	3 weeks		
Fletcher and Harris [1]	1933	10	M	3 weeks		
Fletcher and Harris [1]	1933	10	M	1 week		
Fletcher and Harris [1]	1933	14	M	6 weeks		
Fletcher and Harris [1]	1934	4	M	4 weeks		
Fletcher and Harris [1]	1935	3	M	5 weeks		
Edgar and Syverton [9]	1936	15	F	Discharged after 10 days		Sodium salicylate used in treatment
Chick and Witzberger [10]	1936	11	M	Discharged 30th day. Severe oral Vincent's infection		
Fletcher and Harris [1]	1937	6	F	5 days		
Fletcher and Harris [1]	1937	13	M	7 weeks		
Lever, W. F. [11]	1937	49	M	32 days	Died few months later of carcinoma esophagus	
Rosenberg and Rosenberg [12]	1937	11	M	3 weeks		
Koke [4]	1938	9	M	3 weeks		
Fletcher and Harris [1]	1939	9	F	7 days	Necropsy	
Koke [4]	1939	39	M	5 days		
Koke [4]	1939	8	M	1 month		
Givner and Ageloff [13]	1939	23	M	1 month	Symblepharon	
Givner and Ageloff [13]	1939	4	F	3 weeks		
Ageloff [14]	1940	4	F	20 days		Neoprontosil used in treatment
Fletcher and Harris [1]	1940	9	F	6 weeks		
Lever [11]	1941	35	M	2 months	Conjunctival scarring and corneal opacity	
Fletcher and Harris [1]	1942	9	F	6 days	Died	
Murphy [15]	1943	22	M	4 weeks	Slough glans penis	Sulfadiazine used in treatment
Fletcher and Harris [1]	1943	3	M	3 weeks		
Fletcher and Harris [1]	1943	52	M	2 weeks		Sulfonamide
Fletcher and Harris [1]	1943	7	F	3 weeks		Sulfonamide
Fletcher and Harris [1]	1943	16	M	3 weeks		Sulfadiazine
Levy [16]	1943	7	M			
Kove [17]	1944	19	M	26 days		Sulfadiazine
Kove [17]	1944	19	M	86 days		Sulfadiazine and penicillin
Erger [18]	1944	23	M	3 months	Bilateral corneal scarring	Sulfadiazine

Discussion

It may be of some significance in view of the unknown etiology that two cases of this rare syndrome have been admitted to one service within a period of one month occurring during the mild influenza epidemic of 1945. The disease may be an allergic reaction to bacteria without actual invasion of the microörganisms, or it may be of viral origin. The pathology is an intra- and intercellular edema of epithelium, with subsequent swelling of the squamous cells, widening of epithelial lymph spaces, formation of small vesicles and then their confluence with clinical vesiculation.[19] The lower layers of the cutis and subcutis are not involved.

This syndrome is more commonly found in Europe, Italy, the Balkan states, and Turkey, but seems to be on the increase in this country. Numerous degrees of eye involvement have been reported ranging from simple catarrhal conjunctivitis to ocular destruction. Whatever its designation it must be recognized as a condition in which the only serious end result is possible destruction of sight. The conjunctivitis is potentially destructive. It may have to be differentiated from foot and mouth disease, pemphigus vulgaris, varicella, vaccinia, and diphtheria.

Summary

Two more cases of the Stevens-Johnson syndrome may be added to the published cases. Bronchopneumonia with enlargement of the hilar glands occurred in both cases. The falling off of the nails of the digits which occurred in case 2 was mentioned in only one of the reviewed cases. Both cases were treated with penicillin; in comparison with the outcome of the published cases its effect upon the disease itself did not seem remarkable, although it no doubt was effective treatment for the pneumonia. The purulent conjunctivitis is the alarming symptom. The disease seems to be the expression of a systemic infection. The etiology is unknown.

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COARCTATION OF THE AORTA *

By Joseph R. Fontanetta, M.D., *Brooklyn, N. Y.*

Coarctation of the aorta is infrequently encountered clinically, although it is one of the most common congenital cardiac anomalies. In Abbott's series of 1000 cases of congenital cardiovascular defects, this condition was noted in 142 instances, being the primary lesion in seventy-nine. Baugh [1] places the incidence as high as one per thousand in the general population, while Blackford [2] maintains from his study of necropsy material that the frequency approximates one in 1550 cases. Similarly Levine [3] has stated that one in every 2000 persons in the general population has this abnormality. Abbott and Weiss [4] have emphasized the frequency with which this lesion is overlooked clinically. Undiagnosed cases are usually considered to be instances of essential hypertension, an error which stems principally from the fact that coarctation of the aorta is not generally kept in mind. Palpation for interscapular pulsation and measurements of the blood pressure in the upper and lower extremities would often establish the diagnosis in these cases. Occasionally in cases of coarctation hyperthyroidism has been erroneously diagnosed leading to unnecessary surgery.

A review of the literature indicates that the majority of reported cases of coarctation of the aorta were diagnosed either after cardiac symptoms had become manifest, or at necropsy. Emphasizing this point Blackford [2] in 1928 stated that of about 200 cases in adults already reported, only 19 were definitely recognized

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clinically. Lewis [5] similarly found that aortic coarctation is frequently not diagnosed during life and admitted that several cases under his observation went unrecognized for some time before diagnosis was established. Since the advent of World War II, however, it has been possible to diagnose coarctation of the aorta in many instances by means of the routine chest roentgenogram required of every examinee before entrance into the armed forces.

Abbott and Weiss [4] classify cases of coarctation of the aorta into the infantile and adult types. The first or infantile type, which is relatively rare, consists of narrowing of the isthmus of the aorta, more specifically that part between the left subclavian artery and the ductus arteriosus. It is usually associated with other important anomalies and is incompatible with long life, the infant usually dying before the ninth month. In the adult type of aortic coarctation there is a very localized constriction of the aorta at or most often just below the insertion of the ductus arteriosus. This type is much more common than the infantile type and less serious. Life expectancy generally ranges from the second to the fifth decade, although one patient has been reported to have lived to the age of 92 years. The causes of death in the adult type of coarctation of the aorta are usually cardiac failure, cerebral hemorrhage, dissecting aneurysm of the aorta and bacterial endocarditis. It is apparent that early recognition of aortic coarctation may prolong life by measures directed toward the prevention of these cardiovascular complications.

All grades of narrowing of the aorta occur, from that which is so slight that it can scarcely be seen on careful necropsy examination to complete local aortic obliteration. To compensate for the significant degrees of stenosis, there develops early in life a collateral circulation between the branches of the aorta, above and below the constriction. Some authors are of the opinion that the mechanical factor of stenosis is responsible for the elevation of the blood pressure in subjects with coarctation of the aorta. Rytland,[6] however, believes from his experimental evidence that the hypertension is actually due to renal ischemia resulting from the vascular constriction, being similar to the Goldblatt type of hypertension. Brotchner,[7] on the other hand, embraces the view that hypertension in aortic coarctation is due solely to the mechanical stricture of the aorta. He bases this hypothesis upon experiments in dogs in which he found that the hypertension was not due to a renal pressor substance.

At the Merchant Marine Medical Center in New York City we have seen two cases in which a presumptive diagnosis of coarctation of the aorta was made clinically, and confirmed by roentgenologic study.

Case 1. On December 9, 1944, a white merchant seaman, aged 19, had his initial physical examination before sailing. This young man's family and past history was negative. Previously he had been seen by several doctors who had found him physically fit. He gave no history of rheumatic fever, tuberculosis, syphilis, or nephritis. There were no complaints of dyspnea, cough, headache, syncope, vertigo, tinnitus, or pain in the legs.

Physical examination revealed a well built young man who showed no cyanosis of fingers or lips and no clubbing of the fingers. His examination was essentially negative except for his cardiovascular system. His heart rhythm was regular, and his pulse rate at the time of the examination was eighty-six. On percussion there was no left ventricular enlargement. No thrills were felt. On auscultation there was heard a slight systolic murmur at the apex and the base. Pulsations were felt

in the intercostal spaces over the left upper chest, but none was found in the interscapular region. There were no femoral pulsations. Blood pressure in the right brachial artery was 190 mm. Hg systolic and 100 mm. diastolic, in the left 192 mm. Hg systolic and 100 mm. diastolic. Blood pressure in the right femoral artery was 100

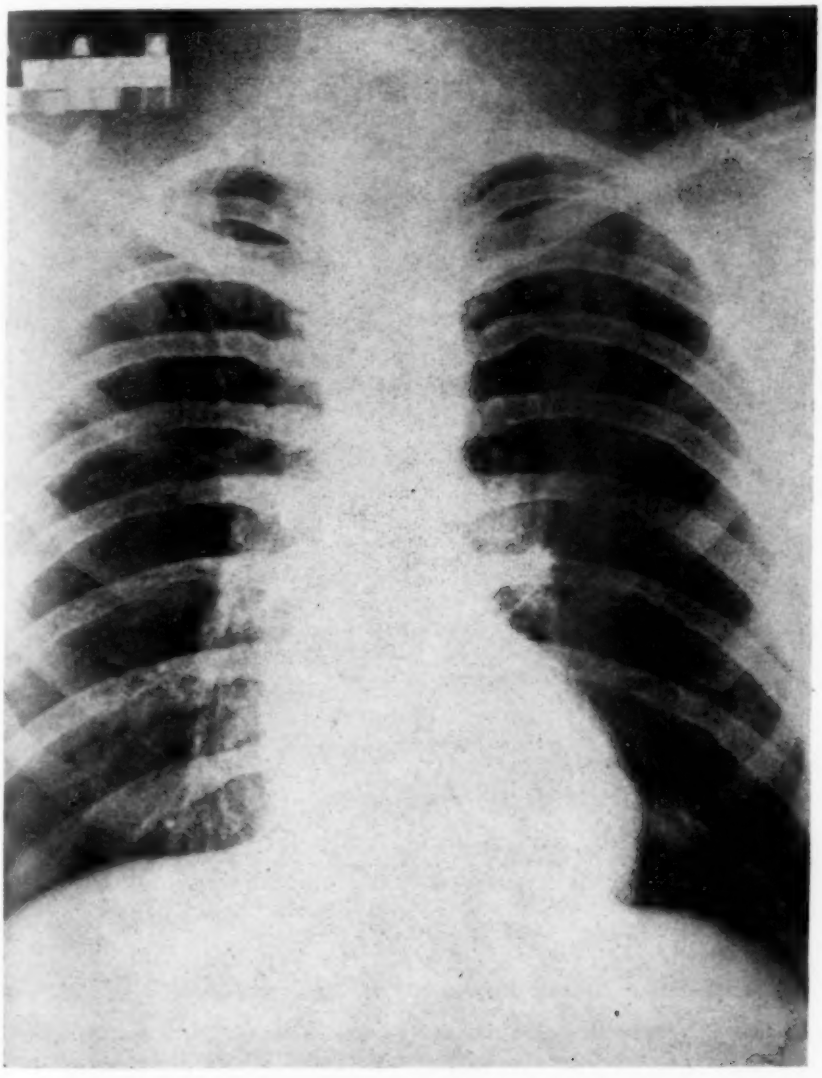

FIG. 1. *Case 1.* Scalloping of the lower rib margins on both sides, prominence of the left ventricle and a small aorta.

mm. Hg systolic and 60 mm. diastolic, and in the left 102 mm. Hg systolic and 64 mm. diastolic. Urinalysis was negative as well as the Kahn test. A presumptive diagnosis of coarctation of the aorta was made, and a chest roentgenogram was taken. The findings indicated scalloping of the lower rib margins on both sides, prominence of the left ventricle and a small aorta (figure 1).

Case 2. A 21 year old white merchant seaman before sailing had his initial physical examination at the Merchant Marine Medical Center. His history was essentially negative. Physical examination revealed a well built young man with negative physical findings except for his cardiovascular system. His only cardiac finding was a slight systolic murmur over the aorta, and hypertension. His blood pressure in the right brachial artery was 200 mm. Hg systolic and 120 mm. diastolic and in

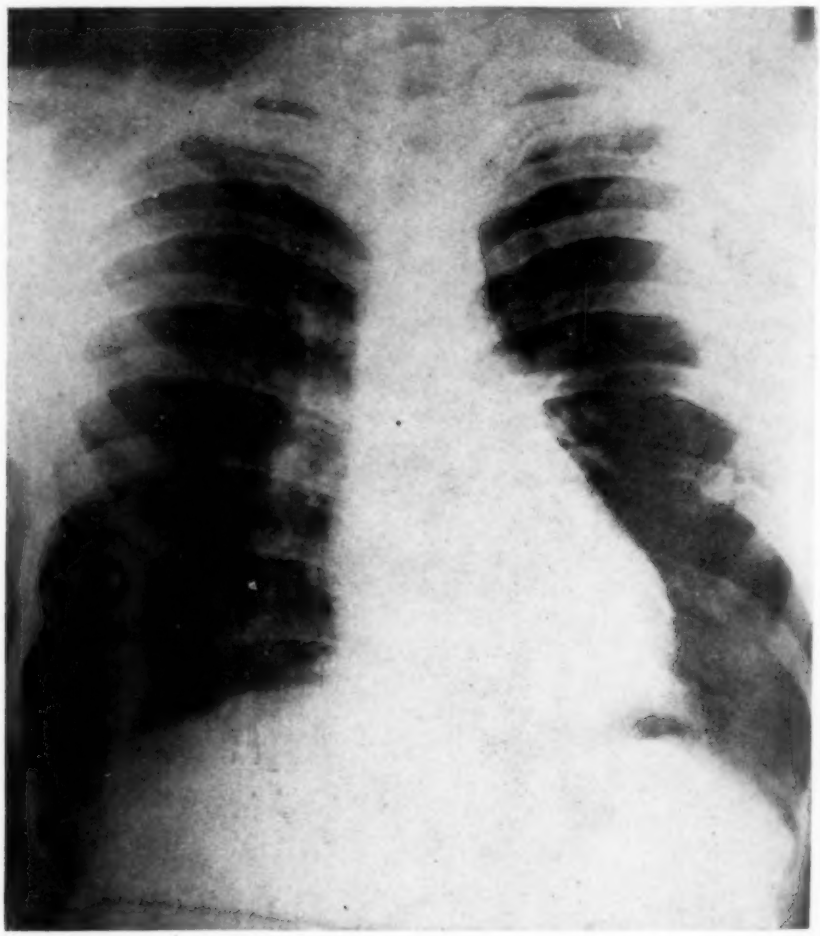

FIG. 2. *Case 2.* Scalloping of the ribs on both sides, a narrow aorta and slight prominence of the left ventricle.

the left 196 mm. Hg systolic and 114 mm. diastolic. Further investigation revealed a blood pressure of 120 mm. Hg systolic and 90 mm. diastolic in the right femoral artery and 114 mm. Hg systolic and 94 mm. diastolic in the left. No pulsations along the scapula were found. The femoral pulse could not be elicited. Urinalysis was negative. A presumptive diagnosis of coarctation of the aorta was made and a chest roentgenogram was taken. The findings showed scalloping of the ribs on both sides, a narrow aorta and slight prominence of the left ventricle (figure 2).

Summary and Conclusions

1. Coarctation of the aorta is a common congenital vascular anomaly which is frequently unrecognized clinically.

2. The pathogenesis of elevated blood pressure in this condition has not been clearly established. Some authors believe that the mechanical effect of the stenosis of the aorta is the cause of the hypertension, whereas others try to connect it with the Goldblatt type of hyperpiesia.

3. A review of two cases of coarctation of the aorta is given with their case histories.

4. It is concluded that every case of hypertension in a young adult should be investigated with the possibility of coarctation of the aorta kept in mind.

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ONCHOCERCIASIS: CASE REPORT *

By Joseph M. Gannon, Major, M.C., A.U.S., *Plainfield, New Jersey*

Onchocerciasis is a tropical disease found only in sharply circumscribed areas of Central America and Africa. It is characterized by the occurrence of subcutaneous tumors or nodules due to the presence of the nematode *Onchocerca volvulus*. The disease is virtually confined to the colored race. Stitt [1] reports that in Africa infection in white men is rare, only some 20 cases having been reported. The case here presented occurred in a white male and the diagnosis was made while he was a patient in a hospital in England.

Case Report

A 32 year old, white, Free French sergeant was wounded in France in August, 1944 and was brought to England for treatment of his injured elbow. Physical examination revealed that in addition to a wound of the elbow he had a mass in the left rectus abdominis muscle below the umbilicus; this mass was considered to be a ventral hernia. The patient reported that this mass had been present for many years and that it had not undergone any change in size. On November 14, 1944 a spherical tumor, 1.5 cm. in diameter, was removed from the posterior sheath of the left rectus abdominis muscle. Except for a soft yellowish area at one pole it appeared on section as a typical dense white fibroma.

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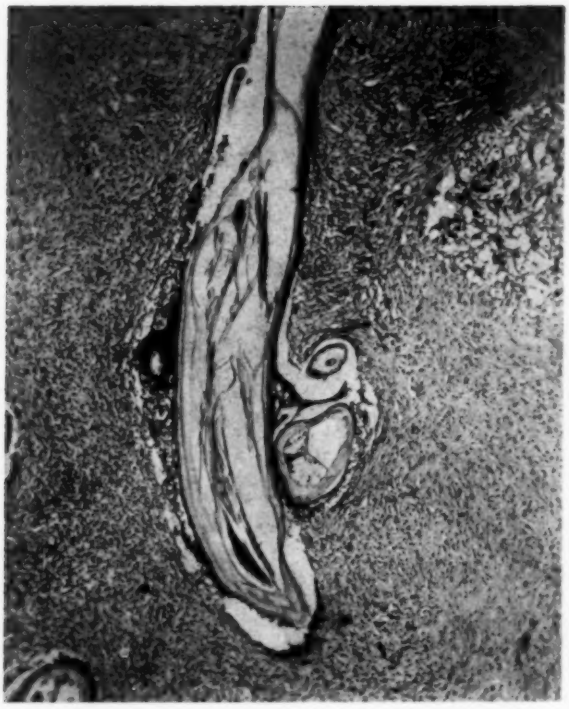

FIG. 1. Photomicrograph of fibroma with sections of *Onchocerca volvulus* cut transversely and longitudinally. × 50.

FIG. 2. Photomicrograph showing microfilariae within the adult *Onchocerca volvulus*. × 300.

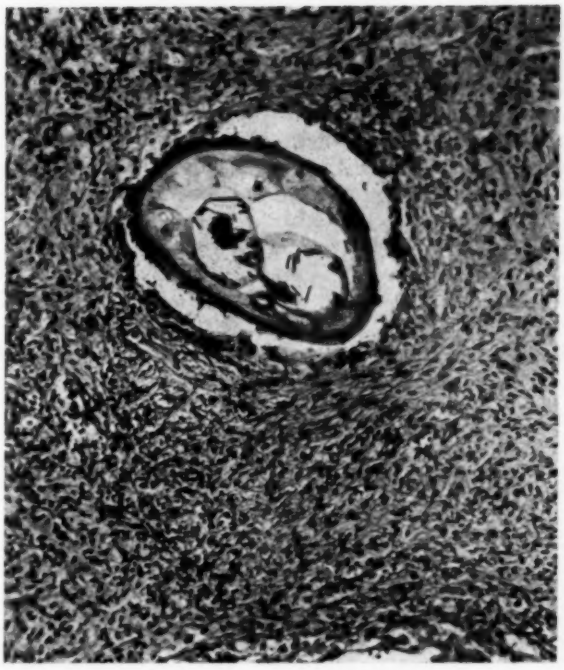

FIG. 3. Photomicrograph of transverse section of *Onchocerca volvulus* with surrounding inflammatory reaction. × 100.

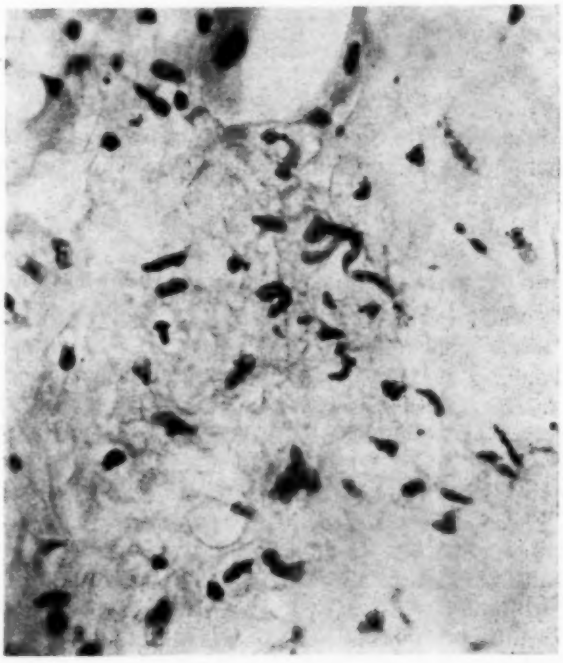

FIG. 4. Photomicrograph showing microfilariae free in the tissue of the nodule. × 300.

Microscopic examination of the histological preparation of this fibrous tumor revealed the adult filarial worm, *Onchocerca volvulus,* surrounded by dense fibrous connective tissue (figure 1). Contained in it were myriads of microfilariae (figure 2). In some areas the microfilariae were free in the fibrous tissue. Around some of the portions of the adult worm there was marked inflammatory reaction with infiltration of the tissues by polymorphonuclears, round cells, and eosinophiles. In some areas of the section the eosinophile infiltration was quite marked.

The blood smear on November 18, 1944 showed 17 per cent eosinophiles. There were no other nodules present and there was no history of past or recent eye disease. Ophthalmological examination was negative. This soldier's tropical service was significant as it took him during the period 1931 to 1944 into Gambia, Congo, and Cameroon; these are areas where onchocerciasis is endemic.

Discussion

The clinical significance of African onchocerciasis is usually not great except that it is a cause of unexplained eosinophilia. The microfilariae migrate in the subcutaneous tissues of the host for varying distances but, except for the patient who is specially sensitive to the parasite or its toxins, they do little harm. In the Central American type, in which the lesions tend to be located on the head, the microfilariae are prone to invade the eyes and cause iridocyclitis, keratitis, pannus formation, and eventual blindness. In the African type, in which the lesions tend to be located on the trunk, involvement of the eyes is exceptional.

The disease is transmitted by flies of the genus *Simulium*. One may reasonably speculate that this is an old disease in which parasitism has been successful to the point where infection results more in inconvenience than in disease. Treatment consists in removal of the nodule. Following this the microfilariae in the tissues survive for a while but they eventually die.

Summary

A case of onchocerciasis is reported which occurred in a young adult white male of French nationality and which was diagnosed while he was a patient in a hospital in England.

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ANAPHYLAXIS TO THE INJECTION OF NICOTINIC ACID (NIACIN); SUCCESSFUL TREATMENT WITH EPINEPHRINE *

By Louis Pelner, M.D., *Brooklyn, N. Y.*

An anaphylactic reaction to nicotinic acid has not been previously reported in the literature, although sensitivity to the drug has been noted before. The present widespread use of nicotinic acid, both as a vitamin and as a drug, makes

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reports of these accidents mandatory, because they will undoubtedly be experienced by others. The morbidity can probably be avoided by a careful questioning of the patient before the injection of nicotinic acid is given. In our cases, the usual treatment for anaphylactic shock was sufficient to overcome the symptoms in these patients.

Rachmilewitz and Glueck [1] described the occurrence of an urticarial dermatitis with flushing of the face and severe itching in a patient with pellagra after he had taken two 50 mg. doses of nicotinic acid orally. Chen, Rose and Robbins [2] found no irritant effect from a 1 per cent solution of nicotinic acid injected intradermally. In spite of this, Watrous [3] reported four cases of severe itching and diffuse erythema of the skin in industrial workers exposed to nicotinic acid. Other workers handling nicotinic acid under the same circumstances showed no reaction. Powdered nicotinic acid rubbed into a patch of skin of some of the workers caused itching and erythema, but this result was not evident in others. There was no correlation between smoking and the susceptibility to dermatitis. It must certainly be that some of the workers were allergic to nicotinic acid and some were not.

Nicotinic acid (niacin), one of the B vitamins, has come into widespread use as a drug, because of its vasodilating properties. Especially is this true in the treatment of Menière's syndrome and certain cases of migraine headache. In some cases of these conditions it has had an extremely salutary effect. Intravenous injections of an appreciable amount of nicotinic acid causes in nearly all individuals a bitter taste on the tip of the tongue in about 17 to 18 seconds. This may be considered to be the arm to tongue circulation time of the nicotinic acid. In about one minute a widespread flush appears all over the body. This may last for two or three hours. This flush is desirable and is the basis for the use of nicotinic acid as a drug. The flush of the skin is considered presumptive evidence that the blood flow is increased in the internal structures as well. In the case of the ingestion of tablets of nicotinic acid, the flush may appear irregularly in different individuals and comes on after several hundred milligrams of nicotinic acid are taken. Nicotinic acid amide does not give a flush, no matter how much is taken.

The flush described above is the usual reaction to nicotinic acid given intravenously, and besides being somewhat disagreeable, entails no further difficulty. If after the first or after a subsequent injection of nicotinic acid, the patient develops dizziness, a soft, rapid, thready pulse, a spasmodic cough, a sensation of choking and collapse, it is safe to assume that an anaphylactic shock has occurred. In the two cases about to be described, both patients experienced allergic reactions to an oral dose before receiving the intravenous dose which precipitated the anaphylactic shock.

Case Reports

Case 1. R. C., a 34 year old pregnant woman, was sent for study by her obstetrician because of an extremely reddened and sore tongue. This condition was present in spite of the use of nicotinic acid amide, 150 mg. daily, and riboflavin, 15 mg. daily. Because of the possibility of poor absorption from the intestinal tract 25 mg. of nicotinic acid were given intravenously. The product used contained 50 mg. of nicotinic acid per c.c. as the monoethananolamine salt. Within two minutes, the patient became dizzy, developed extreme shortness of breath and a short spasmodic cough.

The pulse was 110 per minute, thready and somewhat irregular. The blood pressure registered 90 mm. Hg systolic and 60 mm. diastolic, the respirations were 36 per minute and the rectal temperature was 98° F. The patient was gasping for breath and was in collapse. Five minims of epinephrine 1/1000 solution was given intramuscularly. There was some relief of the oppressive symptoms, but these recurred in about 20 minutes, and required the same dose of epinephrine to be given again. The patient had been placed on the examining table and was kept warm. Although she reacted well, she was hospitalized for the night. She required no further treatment. The next day the patient was skin tested with 0.05 c.c. of a 1:20 dilution of the material that was used for the intravenous injection. A fairly large wheal with a surrounding erythema occurred in five minutes.

Careful questioning of the patient revealed that each time a nicotinic acid amide tablet had been taken by mouth, her lower lip had become swollen. This was not known to me at the time of administering the injection. This patient had never had any previous allergic symptoms of a definite nature, although she did have a history of migraine headaches which might conceivably have had an allergic background. It should be noted that this patient had only one injection of nicotinic acid. The sensitization came about apparently through previous medication with nicotinic acid amide by mouth.

Case 2. R. K., female, aged 25 years, complained of severe unremitting left-sided headaches that lasted over a period of 10 days. The headaches were not accompanied by nausea or vomiting. This patient also suffered from ragweed hay fever. No organic disease could be found to account for the severe headaches. She presented some personality problems such as overprotection by her relatives and a feeling of guilt and insecurity over an impending trip planned in order to break away from her family. Medications of various sorts had had no effect on the headache. Injection of 1 c.c. of procaine into some tender spots in the muscles of the right occipital region relieved the headache immediately, but the pain returned within an hour.

It was decided to try nicotinic acid by mouth, 50 mg. three times a day and intravenously as well, in advancing doses. Intravenous therapy with the same preparation used in the first case was started with a dose of 5 milligrams. There was no flush reported by the patient. In all patients previously given this medication a flush was obtained with this dose intravenously. At the time, this fact did not occasion any suspicion of an altered reactivity to the drug. The patient was given 10 mg. the next day, and 15 mg. on the succeeding day. The headaches were not relieved. The patient presented no untoward response, except that the flush was not obtained. It is uncertain what meaning could be attributed to this lack of an expected response. On the fourth day, 20 mg. of the drug were given. Within several minutes, the patient became dizzy, started to cough and choke and went into shock. The blood pressure reading was 80 mm. Hg systolic and 70 mm. diastolic, the pulse rate was 100 and the pulse was thready. The rectal temperature was 98° F. An intramuscular injection of 6 minims of epinephrine was given immediately. This required repetition in 15 minutes because of the return of the spasmodic cough and the sensation of choking. The patient was taken home after two hours. She required a third injection of epinephrine about six hours after the first injection. When she was visited the following day she was entirely well.

Careful questioning of the patient after the reaction had occurred revealed the pertinent fact that the patient developed dizziness and a slow hacking cough about 10 minutes after the third injection and also about 10 minutes after taking a 50 mg. tablet of nicotinic acid on the night before the reaction. Had this important fact been known earlier, the subsequent injection would not have been given. This patient refused to have a skin test done with nicotinic acid, so that data on this point are unavailable.

Comment

As stated above, anaphylaxis to nicotinic acid has not been previously described, although some cases of sensitivity have been recorded.[1, 3] The fact that nicotinic acid is not a protein is no bar to its acting as an antigen. The simplest explanation of this phenomenon is that the drug acts as a "hapten" which combines with the protein of the host after absorption into the body. This hapten-protein combination forms a new allergen specific for itself and not for the protein of the individual. Once a person or animal is sensitized to the hapten-protein combination, the hapten, e.g. nicotinic acid, alone can cause the allergic reactions. This explains the rapidity with which symptoms occur.[4]

There are several case reports of anaphylaxis, even death, due to thiamin.[5] In one recorded case, symptoms appeared after the first injection of thiamin, which raised the question whether the allergy was inherited or perhaps acquired from thiamin intake in the food or the vitamin by mouth. In the first case that is described in this paper, the patient was apparently sensitized by taking nicotinic acid amide by mouth. She had never taken nicotinic acid before.

Nothing that is stated here should be construed as an attempt to hamper the legitimate use of a worthwhile drug. It is merely desirable to point out that anaphylactic reactions may occur with nicotinic acid, and that the usual methods of treatment of anaphylactic shock are useful in coping with this condition. In both our cases, epinephrine in the usual dosage was effective in overcoming the anaphylactic shock. However, this must be given immediately, because by analogy with some of the cases of thiamin allergy, death might otherwise eventuate.

An even more important factor is the possibility of prevention of the reaction. If a patient has been on nicotinic acid or nicotinic acid amide therapy and an injection of nicotinic acid is projected, the patient should be quizzed as to possible sensitivity before the injection is given. If several injections are given, questions as to sensitivity should precede each injection. This warning applies even more definitely to patients who are allergic to other substances. In both of our cases the morbidity could have been avoided if the possibility of allergy to nicotinic acid had been entertained and appropriate questions asked. An intracutaneous test with 0.05 c.c. of a 1:20 dilution of the material to be injected may, if a positive test is obtained, indicate sensitivity. Further work on this point appears to be indicated.

Summary

1. Two cases of anaphylactic shock caused by sensitivity to nicotinic acid (niacin) are described.

2. The usual treatment with epinephrine intramuscularly was effective in relieving the symptoms in both cases.

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A CASE OF FULMINATING MENINGOCOCCEMIA EXHIBITING THE WATERHOUSE-FRIDERICHSEN SYNDROME AND DEMONSTRATING THE VALUE OF CORTICAL EXTRACT ADMINISTRATION *

By H. A. GRUBSCHMIDT, M.D., G. C. GRAHAM, M.D., and E. C. JESSUP, M.D., F.A.C.P., *Hempstead, New York*

PRATT-THOMAS in 1945 [6] reviewed 184 cases of fulminating meningococcemia with eight recoveries. Prior to 1940, all cases were uniformly fatal.

This is a case of Waterhouse-Friderichsen syndrome in a 17 year old white female who fulfilled practically all the clinical criteria and, in addition, yielded meningococci on blood culture. She developed gangrene of three extremities and bilateral ulnar nerve paralysis but recovered. The case presents several unusual features.

CASE REPORT

The patient was a 17 year old white female waitress who entered Meadowbrook Hospital on Oct. 12, 1945, with a chief complaint of chills and fever of several hours' duration. On the day preceding her admission, Oct. 11, 1945, at about 3:30 p.m. she complained of a chill which was followed by fever of 102° F. She went to bed feeling she was coming down with the grippe. She continued to have intermittent chills with fever ranging between 102° and 103° F. throughout the night. At 3 a.m. the following morning, when she got up to go to the bathroom, she complained of pains in her legs and difficulty in walking. At 7 a.m. she noticed purple areas on her legs and red pin-point areas on her arms. A local doctor was called who advised immediate hospitalization and she was brought to the hospital by ambulance at 8:45 a.m. Oct. 12, 1945.

Her previous medical history revealed a possible rheumatic diathesis. As a child she had complained of frequent growing pains and epistaxis. There was, in addition, a familial history of rheumatic fever.

On admission physical examination revealed a fairly well nourished white adult girl who appeared acutely ill. Her lips and skin appeared cyanotic, her skin having a dusky color. Her face was puffy. There were petechiae and large and small purpuric areas over the face and body. These, however, were much more marked over the extremities and particularly the lower extremities. The purpuric areas could be

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From Meadowbrook Hospital.

seen to increase in size during the process of examination. Petechial spots were seen also in the mouth, on the hard palate and on the conjunctivae with sub-conjunctival hemorrhage. She was bleeding from the lower lip and gingivodental margins. Her extremities were cool to the touch. The temperature was 102.6° F. The blood pressure was 80 mm. Hg systolic and 66 mm. diastolic and the ventricular rate was 150 and regular. Respirations were 48. The patient appeared very apprehensive and kept biting her lower lip. Although not comatose she was delirious and remained so for several days. Her neck was supple but she had a positive Brudzinski sign. Her deep reflexes appeared to be hypoactive. However, these were difficult to evaluate owing to the presence of muscle spasm. Her thighs and calves were full, tense, and tender. They felt as if there was exudation or extravasation present involving the

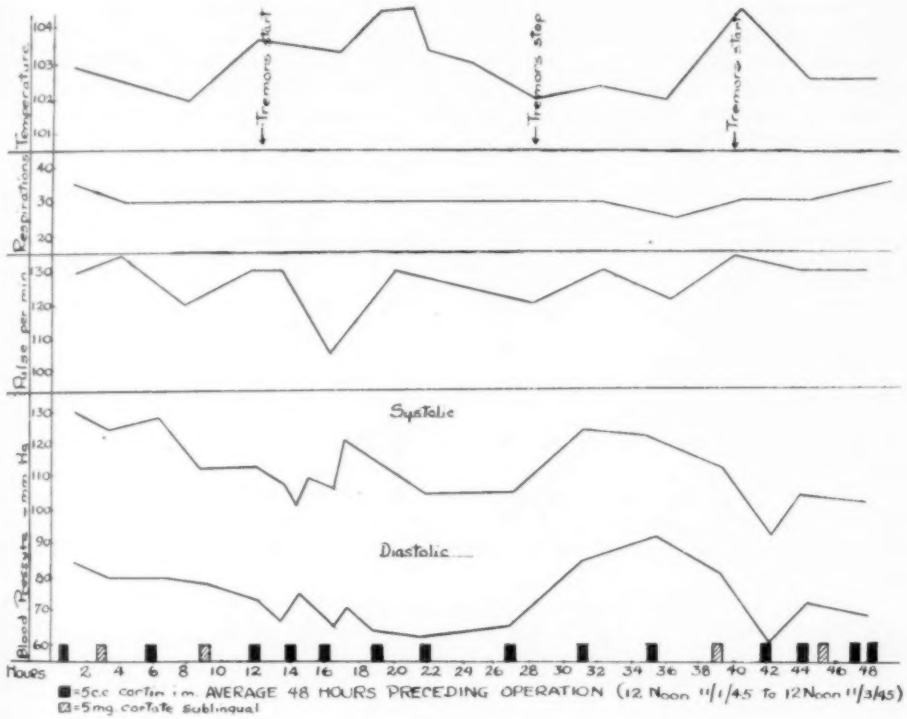
Temperature
Tremors start
Tremors stop
Tremors start
Respirations
Pulse per min.
Systolic
Diastolic
Blood Pressure mm. Hg
Hours
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
■=5c.c. cortin i.m. AVERAGE 48 HOURS PRECEDING OPERATION (12 Noon 11/1/45 to 12 Noon 11/3/45)
▨=5mg. cortate sublingual

FIG. 1.

muscle and subcutaneous tissues. There was generalized muscle tenderness. The remainder of the physical examination was non-contributory. A spinal tap done at the time of admission showed crystal clear fluid at 8 mm. of mercury with 350 red blood cells per cubic millimeter, no white blood cells; sugar, 80 mg. per cent; protein, 53 mg. per cent. The blood count showed 24,000 leukocytes with 90 per cent polymorphonuclears. A provisional diagnosis of meningococcemia with Waterhouse-Friderichsen syndrome was made. The patient was placed in shock position and blood was drawn for chemistry and culture before beginning intravenous therapy. She was given immediately 500 c.c. of 5 per cent glucose and saline containing 50,000 units of penicillin. She received intravenously, 10 c.c. of cortin * and 5 grams of sodium sulfadiazine. Continuous infusions were maintained during the next 10 days.

* Cortin, Upjohn. (Adrenal cortical extract, 50 dog units per c.c.)

During this time she received 3,000 c.c. of whole blood, 2,850 c.c. of plasma, 12,300 c.c. of saline, 3,300 c.c. of 5 per cent glucose and saline, and 4,200 c.c. of ⅙ molar lactate as well as 2,075,000 units of penicillin (roughly 50,000 units of penicillin for every 500 c.c. of fluid) and two grams of sodium sulfadiazine every four hours intravenously (into the tubing). Vitamins also were added to the infusion and given by mouth as well. Cortin was administered during this period intravenously, 5 c.c. every three hours. An attempt was made to maintain a schedule giving 400 c.c. of ⅙ molar lactate a day with 500 c.c. of blood and 500 c.c. of plasma, supplemented with glucose and saline.

Laboratory Examinations. Blood on admission showed non-protein nitrogen 41 mg. per cent; blood sugar, 170 mg. per cent; CO_2 combining power, 41 vol. per cent (drawn on Oct. 17, 1945). Twelve days later non-protein nitrogen was 20 mg. per cent; creatinine, 1.5 mg. per cent; sugar, 94 mg. per cent; chlorides, 462 mg. per cent. The blood culture drawn on the day of admission was reported as positive for meningococci and was negative when repeated on the third hospital day. All succeeding cultures were sterile. Total protein on October 17 was 4.9 gm. per cent with albumin 2.9 gm. per cent and globulin 2.0 gm. per cent. Repeated on October 23, total protein was 4.5, albumin 3.0, globulin 1.5 gm. per cent.

Blood Count:	Oct. 12 (on admission)	Oct. 16	Oct. 22
Hemoglobin		90.4	95
Red blood cells	3,000,000		
White blood cells	24,000	18,000	14,100
Polymorphonuclears	90%	78	74
Lymphocytes	10%	22	22
Monocytes			4

Coagulation time on admission was four and one-half minutes and bleeding time three minutes.

Urinalysis showed many red blood cells on the day following her admission to the hospital. This persisted up to Nov. 9, 1945, in decreasing numbers. The urine showed a faint trace of albumin on admission and continued to do so intermittently since.

Course. The purpuric areas enlarged and became confluent during her first hospital day, eventually covering practically all of the lower portions of her legs and feet. By 8 p.m. on the day of admission her right foot had become quite cold from the ankle down. It was not possible to palpate the dorsalis pedis pulsation on either foot although popliteal pulsations were palpable bilaterally. On the morning of her second day, Oct. 13, 1945, both feet were cold as was also the distal half of the left lower leg. Both feet appeared black, the left more so than the right. Both popliteal pulsations were still palpable. The lower legs and feet seemed greatly swollen and tense. She complained of pain in both lower extremities. The right foot improved somewhat during the day so that in the evening of Oct. 13, 1945, it began to feel warmer. On Oct. 14, 1945, the right foot was quite warm and appeared less dark. The left leg was warm to the ankle. Large subcutaneous blebs began to appear on both lower extremities. On Oct 15, 1945, both feet were warmer and improved in color. The skin of both lower legs and feet, however, continued to form blebs which broke down leaving many raw ulcerated areas. By Oct 30, 1945, there was a proliferation of granulation tissue on the right leg and foot and to lesser extent on the left. The skin of the feet, however, was still in the process of sloughing. Azochloramid soaks were applied to the legs in an attempt to increase the sloughing process and possibly to reduce the growth of redundant granulation tissue. The ulcerating process continued.

so that several days later both legs were devoid of epithelium from the mid-calves to the ankle. Granulation tissue grew in abundance on both legs, more so on the right. The skin of both feet appeared black and gangrenous but did not slough. At this time, her second hospital week, it was noticed that the patient held her hands in the main-en-griffe position. Her legs gradually became grossly infected. She began to have chills and fever ranging to 104° and 105° F. and Nov. 4, 1945, tendons and muscle bellies were exposed. These appeared dark and infected. On Nov. 4, 1945, both legs were packed in ice below the knee and on the following day bilateral amputations, 2 inches below the knees, were performed under nitrous oxide anesthesia. No attempt was made at that time to prepare skin flaps or to close the wounds which were infected. Postoperatively, the stumps were treated with azochloramid soaks and daily irrigations. Skin traction was applied bilaterally.

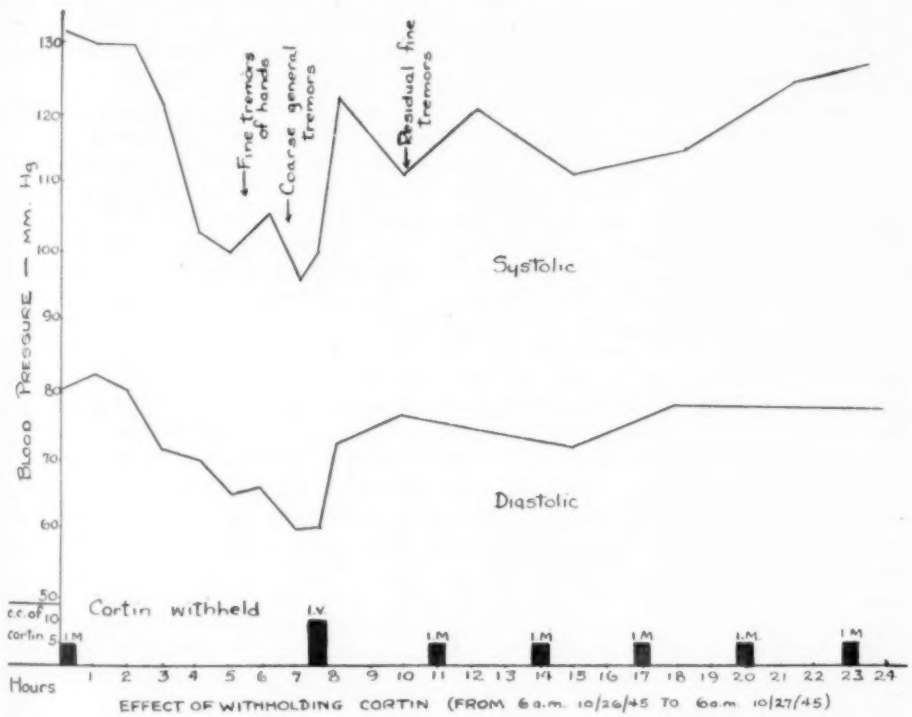

FIG. 2.

The distal phalanx of the index finger of right hand and the terminal phalanx of the right middle finger appeared cold and black on the second day of her admission. By the third day, they were definitely gangrenous and dry. The purpuric areas on her trunk and upper extremities had ulcerated, the smaller ones having healed and the larger ones healing. The blood pressure on admission was 80 mm. Hg systolic and 60 mm. diastolic and remained fairly constant even with rather large doses of cortin until the following day when it rose to 100 mm. systolic and 74 mm. diastolic, increasing gradually to 130 mm. systolic and 80 mm. diastolic on her fourth hospital day. At this point an attempt was made to reduce the cortin from 5 c.c. intramuscularly every three hours to 5 c.c. every six hours with no apparent ill effects. The following day an attempt was made to reduce the cortin to 5 c.c. every 12 hours; however, after seven hours without cortin, the pressure had fallen from 130 mm. systolic and 80 mm.

diastolic to 116 mm. systolic and 65 mm. diastolic and the patient developed generalized somatic tremors. The dose of cortin was again restored to 5 c.c. every 3 hours with an immediate dose of 10 c.c. intravenously, and in one hour the tremors had ceased. The blood pressure, however, continued to fall during the next four hours reaching 104 mm. Hg systolic and 68 mm. diastolic, then it rose again so that by the following morning it was 130 mm. systolic and 80 mm. diastolic. On Oct. 18, 1945, cortin was purposely withheld. After seven hours fine tremors appeared beginning in her hands, spreading to the face, becoming generalized and coarser and being maximal eight and one-half hours following the last dose. During this period, the blood pressure dropped from 130 mm. Hg systolic and 80 mm. diastolic to 110 mm. systolic and 45 mm. diastolic. At this point 10 c.c. of cortin were administered intravenously. Again the tremors disappeared, and the blood pressure began to rise so that it was 112 mm. systolic and 64 mm. diastolic in one hour; seven and one-half hours later it had risen to 130 mm. systolic and 75 mm. diastolic. The diastolic pressure did not reach 80 mm. until the following morning. The pulse rate rose from 108 to 140 with maximal drop in blood pressure and returned to original rate as blood pressure rose. On Oct. 26, 1945 cortin was again withheld. Seven hours from the last dose, the blood pressure had dropped from 132 mm. systolic and 80 mm. diastolic to 96 mm. systolic and 60 mm. diastolic, and the patient exhibited generalized coarse tremors. At this time she complained of a drowsy sensation and a feeling of weakness. Cortin was resumed at this point (10 c.c. intravenously) with the gradual disappearance of the tremors in three hours. The blood pressure rose to 122 mm. systolic and 72 mm. diastolic within the hour and had returned to the original pressure by the following morning. The pulse rate rose and fell inversely to the blood pressure. On each occasion the patient received 5 c.c. of cortin intramuscularly every three hours following the initial dose of 10 c.c. intravenously. A blood chloride level was taken before the cortin was discontinued and was reported as 510 mg. per cent and again before cortin was resumed and was reported as 577 mg. per cent. On Oct. 27, intramuscular cortin 5 c.c. was reduced from every three hours to every six hours and 10 mg. of cortate * were given sublingually every six hours alternately so that the patient received some form of cortical therapy every three hours. This was continued to the time of operation. However, it was noted that the blood pressure tended to be lower with this form of therapy and on several occasions tremors developed; the latter usually occurred when the blood pressure dropped below 100 mm. Hg systolic. Occasional supplemental doses of cortin had to be given to stop the tremors and elevate the pressure. During one of the episodes of generalized tremors and hypotension, a blood sugar determination read 120 mg. per cent. It was further noted that the drops in blood pressure seemed to coincide frequently with sharp elevations in temperature. The night preceding her operation she was given cortin 5 c.c. and sodium chloride 4 gm. per os every three hours with 10 c.c. of cortin intravenously immediately preceding the operation. Cortin was given, 5 c.c. intramuscularly, every three hours following operation as well as saline, plasma, and whole blood. A continuous intravenous drop was maintained for the first four post-operative days during which time she received 7,000 c.c. of 5 per cent glucose and saline, 2,000 c.c. of saline, 2,000 c.c. of plasma and 1,000 c.c. of whole blood. Penicillin was given at the rate of 50,000 units for every 500 c.c. of intravenous fluid along with 20,000 units every three hours intramuscularly. One ampule of synkamine was given daily. On the first post-operative day cortin and cortate were administered alternately every three hours, and the temperature went to 106° F. but dropped rapidly to 102°. On this day her blood pressure tended to be rather low, and tremors were noted almost all day. This is the last time the patient exhibited tremors, and since then her blood pressure has been well maintained. Cortin was decreased gradually and on Nov. 9, the fourth post-operative day, it was discontinued

* Cortate, Schering. (Desoxycorticosterone acetate, 5 mg. per c.c.)

with no apparent ill effects. On Nov. 7 physiotherapy was started in an attempt to improve the function of her hands. Hypesthesia, anesthesia, and paralysis were present in those portions mediated by the ulnar nerves. During the first 10 days of her illness, she ran a fever ranging between 103° F. and 104° F. However, after the infusion was cut on the tenth day, it ranged between 100° and 102° F. and gradually climbed to 104° and 105° F. several days preceding amputation of her legs. Latterly the temperature curve was of a septic type. Following the amputation the temperature gradually dropped and became normal on Nov. 15, 1945. The radial pulse which had been imperceptible on admission could be palpated that same evening and was fairly strong by the second day. Penicillin was discontinued on Nov. 13, 1945, the patient having received a total of 6,060,000 units. She received in addition during her hospital stay, 99 gm. of sulfadiazine, the last 30 gm. being given intermittently after the first 10 hospital days.

Blood Counts:	Oct. 31	Nov. 14
Hemoglobin	95	50%
Red blood cells		3,500,000
White blood cells	8,200	4,000
Neutrophiles	60	60
Lymphocytes	40	40

Chemistry:	Nov. 2	Nov. 8	Nov. 14
Non-protein nitrogen		21	23
Creatinine		1.5	1.5
Sugar	120	95	85
Chlorides			445
Total protein	4.2	4.6	
Albumin	3.2	2.9	
Globulin	1.0	1.7	

Report of Pathologist:* Nov. 5, 1945. *Specimen:* Both legs.

"Specimen consists of two legs which have been amputated just below the knee. The skin of both feet extending from the toes to the region of the ankle joint shows black gangrenous discoloration. From each ankle to the sites of amputation there are large irregular deep ulcers many of which are confluent and replace the greater portion of the skin surface. There are extensive areas of granulation tissue centrally situated in many of the ulcers and superimposed upon these there are broad islands of re-epithelialization. The muscles and tendons of the anterior aspect of the right ankle are exposed. The involved skin appears to extend up to the very line of surgical transection. Section through the major vessels just distal to the line of transection shows no evidence of grossly visible thrombosis or inflammation of the major veins or arteries at these sites. However, in the right leg just below this area the posterior tibial vein contains an elongated well formed but non-adherent thrombus which is dark red and presents gray surface striations. The other large vessels more distal to these areas do not appear to be involved. On section into the ulcerated areas of the skin and subcutaneous tissue the underlying connective tissues appear indurated and edematous. Beneath each ulcerated zone the veins appear to be distended and occluded by soft grayish-brown and dark red blood clots, some of which are loosely adherent while others are easily dislodged. The arteries, however, are not affected. A few areas in the right leg present bright, opaque yellow, irregular zones up to 3 cm. in diameter resembling infarcts of the subcutaneous fat with thin bright red hemor-

* Dr. Theodore J. Curphey, Chief of Department of Pathology.

rhagic borders. The muscle and deep fatty tissues are softened and show reddish-brown discoloration. On section into the under surface of both feet the gangrene appears to involve the entire skin layer while the underlying muscle and fat show reddish-brown discoloration. The bones and joints do not appear to be involved.

"Microscopic: Sections show extensive chronic productive inflammation of the skin and subcutaneous tissues with interstitial hemorrhage and extensive infiltration of polynuclear cells. Many of the areas of skin and subcutaneous tissue appear gangrenous and stain poorly, while the major arteries and veins show no evidence of thrombosis. Many of the central vessels, especially the veins, appear to be occluded and distended by blood clots with evidence of organizing change at the periphery. In

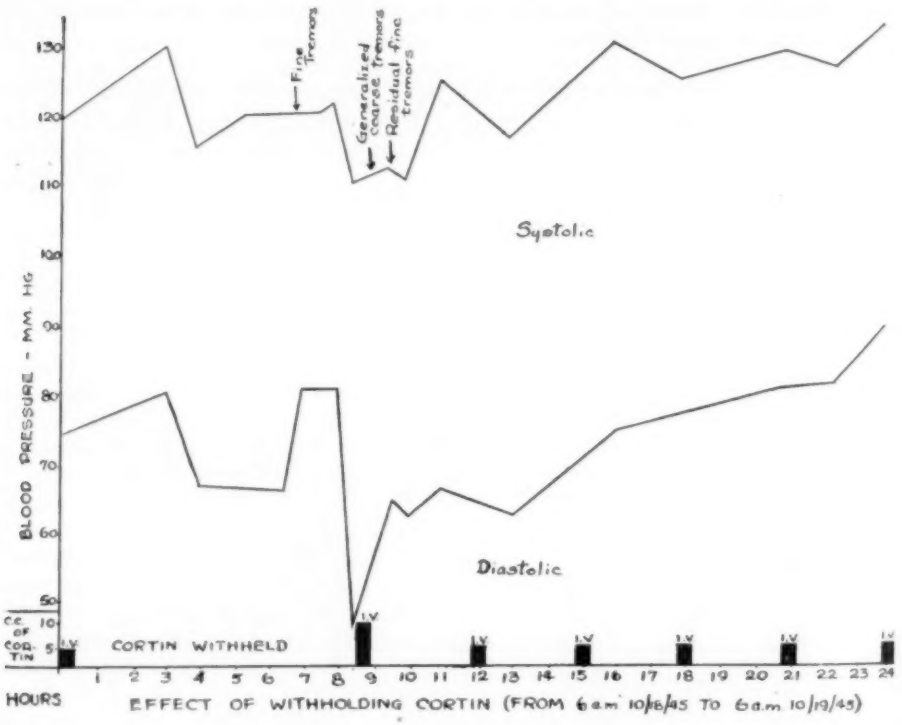

FIG. 3.

some sections the small arteries are also occluded and show evidence of similar organization of the blood clots. A prominent feature is the muscular hypertrophy of many of the arterioles which, however, show no evidence of blood clot.

"Diagnosis: Gangrene of skin secondary to organizing septic arterial thrombosis with coincident arteriolar medial hypertrophy."

DISCUSSION

Ectodermal necrosis and slough have been reported [2, 7] and also gangrene involving several toes requiring amputation.[4] The case presented here exhibited numerous areas of ectodermal slough involving the trunk and all extremities, gangrene of the skin of the feet and both lower legs and the distal half of the right index finger and terminal phalanx of the right middle finger. The pathological

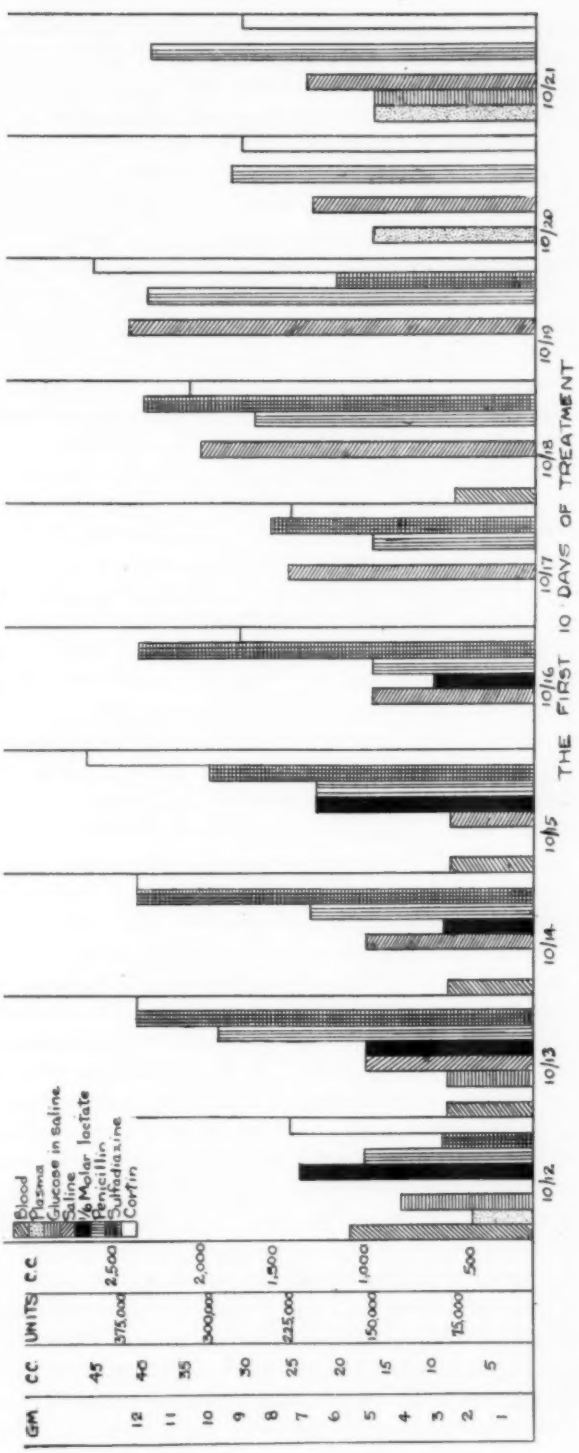
GM
CC.
UNITS
C.C.
Blood
Plasma
Glucose in Saline
Saline
⅙ Molar lactate
Penicillin
Sulfadiazine
Cortin
10/2
10/3
10/4
10/5
10/16
10/17
10/18
10/19
10/20
10/21
THE FIRST 10 DAYS OF TREATMENT

FIG. 4.

report noted the presence of septic arterial thrombi and arteriolar medial hypertrophy. The latter would be of therapeutic interest if the hypertrophy could be interpreted as arteriolar spasm which conceivably could add to the extent and severity of tissue necrosis. Such an assumption could not be made from a microscopic examination alone.

The patient further presented involvement of both ulnar nerves. This became apparent about the end of the first week and manifested itself by the main-en-griffe position of both hands with hypesthesia, anesthesia and paralysis of those portions mediated by the ulnar nerves. At this writing, two months after onset, she gives no evidence of return of function although there is some lessening of the degree of anesthesia. We believe this to be the first reported case showing peripheral nerve involvement.

Of particular interest was the relationship between blood pressure and cortical extract administration. On three separate occasions, cortical extract was withheld for variable periods. On each occasion, the systolic and diastolic pressures started downward two to three hours following the last injection and reached a maximum drop in seven to eight and one-half hours with the patient exhibiting fine tremors of the hands spreading to involve the face and general musculature and becoming coarser so that at the end of an hour they were quite coarse. On at least one of these occasions, Oct. 26, she developed subjective complaints of drowsiness and weakness. The blood pressure was permitted to continue downward from one to four hours before the administration of 10 c.c. of cortin intravenously. Response was manifested by an upward trend of systolic and diastolic pressures within one hour, requiring from eight to 16 hours to return to the original level while receiving 5 c.c. of cortin every three hours. The systolic and diastolic pressures responded similarly. Sodium and potassium determinations were not made owing to limitation of laboratory facilities.

It was noted that when parenteral cortin was alternated with cortate sublingually every three hours, the patient tended to maintain a somewhat lower daily blood pressure than when receiving 5 c.c. of cortin every three hours. At times the systolic pressure fell below 100 mm. and then tremors would appear. The latter could be made to disappear with supplementary parenteral doses of cortin. It was noticed that fall in blood pressure frequently coincided with marked elevation of temperature. Because cessation of tremulousness and rise in blood pressure followed administration of cortin fairly consistently, it was felt that hypotension and tremors were expressions of, at least, relative adrenal cortical insufficiency. It was thought that the signs and symptoms of cortical insufficiency constituted a non-specific reaction to sepsis and toxemia at first due to meningococcemia and later to gangrene and gross infection of the lower extremities. The patient was taken off cortin therapy on her fourth post-operative day and during the ensuing 30 days maintained her blood pressure, displaying no tremulousness or evidences of adrenal cortical insufficiency. It is inconceivable that destruction of the adrenals, in whole or in part, which could result in adrenal cortical hormone insufficiency for 25 days could be reversed within a period of four days following operation. Thus, hypotension and tremulousness were interpreted as expressions of relative adrenal insufficiency precipitated by sepsis and toxemia and aggravated by hemorrhagic adrenalopathy. As there appeared to be a fairly constant relationship between high fever and hypotension and

tremulousness, it was considered that altered physiology based on high fever with accelerated metabolic rate would be a major factor in precipitating relative cortical hormone insufficiency. Since one of the essential functions of the cortical hormone is considered to be that of catalyzing oxygen utilization,[3] an increased oxygen need would tend to make manifest latent impaired adrenal cortical function. It was felt that cortin extract administration played an important rôle in the survival of this patient and probably should be considered indispensable in the treatment of this syndrome.

Of some interest is the relatively high blood sugar present on admission. McGavack [8] reported a similar finding in his case which he explained on the basis of a trigger mechanism releasing adrenalin-like substances into the circulation with secondary elevation of blood sugar.

The blood sugar determination made at the height of a period during which the patient was exhibiting generalized coarse tremors read 120 mg. per cent so that hypoglycemia could not have been the cause. The tremors might be explained on a basis of secondarily impaired carbohydrate metabolism with resultant muscle weakness [8] and could be relieved by administration of cortin. The fact that the patient had adequate supplementary daily doses of sodium chloride suggested that loss of sodium was not a factor in the drop of blood pressure and appearance of tremors. Even if sodium was being lost, this is a relatively slow process [1, 5] and would not become clinically manifest within eight hours. Furthermore, when cortate (desoxycorticosterone acetate) was being alternated with cortin, the patient maintained lower blood pressures than when maintained on cortin alone. Since desoxycorticosterone acetate is concerned with stabilizing electrolyte balance, the lower blood pressures present during its administration would militate against sodium loss as a cause of hypotension and tremors; however, it is true that there is a tendency toward irregular absorption with sublingual administration of cortate which must be taken into consideration.

Summary

1. A case of Waterhouse-Friderichsen syndrome with recovery in a 17 year old white female exhibiting almost all the clinical criteria with the presence of meningococci in culture of the blood.

2. Present also were multiple areas of ectodermal necrosis and slough over the trunk and extremities with gangrene of the distal half of the right index finger and tip of the right middle finger. In addition, there was massive gangrene of the skin of the feet and lower legs requiring bilateral amputation and exhibiting microscopically arterial septic thrombi and arteriolar medial hypertrophy. In addition, there was present involvement of both ulnar nerves with hypesthesia, anesthesia and paralysis.

3. Hypotension and tremors were interpreted as evidences of relative adrenal cortical hormone insufficiency precipitated by sepsis and toxemia and aggravated by hemorrhagic adrenalopathy, and which could be induced during the course of illness by withholding cortin therapy.

4. The appearance of clinical manifestations was explained as due to altered physiology in which high fever with accelerated metabolic rate and resultant increased oxygen requirement made manifest latent adrenal cortical insufficiency.

5. Cortical extract is considered an indispensable adjunct of the treatment of Waterhouse-Friderichsen syndrome. Desoxycorticosterone acetate is probably ineffective.

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Erratum

On page 242 of this issue an error occurred in the column headed "Cases." The corrected table is reprinted here.

Table III

Duration of Symptoms at Examination at Clinic

Years	Cases
Less than 5	311
5–9	342
10–14	201
15–19	90
20 or more	74
Total	1,018*

* In 17 cases duration of symptoms was indeterminate.

EDITORIAL

THE EXPANDING INFLUENCE OF THE SCHOOLS OF MEDICINE

IN THE reorganization of medical education in the United States which has occurred since the beginning of the century one may distinguish a period characterized by the integration of the medical schools with Universities, and by a tendency towards their isolation from the rest of the medical community. The dominant advances in this period have been the development of the medical sciences and of the clinical specialties.

The concentration of the schools upon the basic medical sciences and upon the problems of human disease led to alterations in the composition of the medical faculties and also for a time to a change in emphasis in medical education. It was early recognized that the faculty in the departments of the basic medical sciences must devote full time to their task if the work of these departments was to result in significant new contributions to medicine. Gradually the same reasoning came to be applied, in part at least, to the clinical departments. In all the major schools the number of junior full time clinical teachers and investigators has been increased and in a number of schools the heads of clinical departments are on a full time basis. In the selection of such full time personnel greater emphasis has usually been laid upon the man's aptitude for original investigation than upon his breadth of clinical knowledge and experience.

Inevitably the emphasis upon research led to some restriction of the interest of a major and most influential portion of the faculty in the problems of medical care in the home and in the physician's office, as well as in the increasing rôle of preventive medicine under city, state and federal auspices. In the teaching of medicine the emphasis was almost exclusively upon the structure and functions of the human body and its reaction to disease. The problems of the diseased individual, and the responsibility of the physician as his medical advisor received scant attention. There was in brief a tendency for medical schools to become isolated scientific institutes separated in interests from the practicing physicians and the health officers of their community.

This tendency to isolation did and, to some extent, still does exist; and it has tended to diminish the influence of the schools in a period of rapid changes in the organization of medicine in the United States. In the last twenty years, however, many factors have been operative which are bringing medical schools into closer relationship with the social problems of the sick and the medical problems of their communities and of the nation.

The development of welfare agencies, the growth of medical social service and perhaps most of all the infiltration into medical thinking of the psychiatric point of view have greatly altered clinical teaching. It is interesting to observe the new stress upon the patient as an individual and

the rediscovery in the schools of a fact well known to all successful general practitioners that patients have families and multiple other problems which affect their physical functions. More is being done to follow the patient into the home, and to integrate that portion of his medical care which he receives in the out-patient service or wards of the school with that which is afforded him by the clinics of the Health Department and by the general practitioner of his neighborhood. As progress is made in this direction the school not only extends its influence in the medical work of the community but can offer to its students a more complete view of the problem of adequate medical care for an individual.

The rapid growth of specialization in clinical medicine, combined with the standards set for specialists by the American Medical Association and the national societies of each specialty, has resulted in a greatly increased demand upon the medical schools for residencies and fellowships in the various special fields. The schools in their own interests as medical centers are attempting to develop active subdepartments in each clinical specialty. To do this successfully usually requires an increase in the number of available teaching beds. The solution of this problem has often been met by agreements which give to the school control of the free beds in voluntary or tax supported hospitals. The introduction of teaching and of school standards of medical care into such hospitals enables these institutions to obtain capable house officers and adjunct staff members who might otherwise not be attracted. The development by medical schools of such multiple hospital services is an increasing process. While often presenting great practical difficulties, it has the advantage of expanding the facilities of the school for postgraduate education and for research in new fields. Moreover, it brings the school into many new contacts with the community and greatly broadens its influence.

Another instance of the new extramural activities of the medical schools is to be seen in the close relationships recently developed between certain school departments of preventive medicine and the field work of the local Department of Health. Schools of medicine are usually called upon, moreover, to furnish representatives to all advisory councils connected with the medical programs which receive federal support. The integration of the school with the work of governmental health agencies, city, state and federal, has reciprocal aspects. The facilities of public health agencies are often supplemented by the school and on the other hand funds for certain types of clinical work and research in the schools are often provided by federal grants in aid.

Within very recent times, impelled by the urgency of the situation concerning the medical care of the veterans, the medical schools of this country have upon request assumed responsibility for nominating the attending physicians and consultants to the veterans hospitals in their vicinities. This association of the medical schools with the veterans hospitals has greatly assisted in the truly remarkable increase in prestige of these latter institu-

tions and has made it possible for them to procure many able younger physicians on a full time basis.

In the difficult situation in which the Medical Department of the United States Army now finds itself relative to procurement of specialists for its hospitals in this country, many faculty members of our schools as well as other qualified physicians are serving as consultants to army hospitals. If the army desires to establish more adequate educational advantages in its hospitals to serve as an incentive to recruitment, it is no doubt to the medical schools that it will turn for assistance.

The rapidly broadening influence of our medical schools in their communities and in the nation is evidence of their awareness of the changing conditions in organized medical care and of the increasing scope of their mission in medical education. If this influence is wisely used the schools will contribute greatly to the reorganization of medicine which is in process.

REVIEWS

X-Rays and Radium in the Treatment of Diseases of the Skin. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Director of the Department of Dermatology, New York Post-Graduate Medical School and Hospital, Columbia University, and ANTHONY C. CIPOLLARO, M.D., Assistant Professor of Dermatology and Assistant Director of the Department of Dermatology, New York Post-Graduate Medical School and Hospital, Columbia University. Contributor, HAMILTON MONTGOMERY, M.D., Associate Professor of Dermatology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester, Minnesota. Fourth edition, thoroughly revised. Cloth bound. Illustrated with 321 engravings and 4 colored plates. 668 pages; 15.5 × 24 cm. 1946. Lea & Febiger, Philadelphia. Price, $10.00.

The appearance of a fourth edition of this book indicates that it is meeting a need. It is written primarily for dermatologists and roentgenologists but contains much information of value to internists.

The first 25 chapters are devoted to the history of x-ray and radium; to elementary electricity and the physics of radiation; to factors influencing tissue dosage and tissue recovery; to dangers associated with the administration of x-ray and radium therapy; to various technics of administering these rays; to modes of action of these rays on normal and abnormal tissues; to the effect of x-rays and radium on normal and abnormal tissues; and to acute and chronic radiodermatitis, stressing the great benefits of properly administered irradiation and the tragedy of improperly administered irradiation. These first chapters are written in simple, easily understood language and thoroughly cover all aspects of the modern concepts of radiation therapy. In a previous edition many of these chapters were revised by Dr. Edith H. Quimby, Associate Professor of Radiology, College of Physicians and Surgeons, Columbia University, a well known physicist who has devoted much time to correlating physical factors and biological results. Material added by Dr. Quimby has been retained in this edition.

The authors have stressed the dangers of x-rays and radium in unskilled hands, and to the need for specialized training before attempting to use these agents. They warn dermatologists not to place too much reliance on roentgen therapy. It is commendable that the tone of these chapters is conservatist.

The remaining 16 chapters are devoted to the clinical aspects of many skin diseases and to their treatment by x-rays and radium. In each disease the clinical aspects are adequately covered for a book of this type. The mode of action of the x-rays or radium is discussed. Indications for radiation therapy are enumerated. Advantages and disadvantages of radiation therapy are brought out. Technics and dangers are covered. Many treatises and textbooks on radiation therapy in the past have been sadly deficient in the detail description of technics. In this respect this volume, while still defective in certain instances, does represent a long step toward the goal of a compendium of roentgen technics with each carefully selected on the basis of clinical efficacy, and with each carefully described in detail.

The format is excellent. The numerous illustrations are well selected. The bibliography is quite complete and includes references of as late a date as 1943. The revised edition is recommended without reservation.

W. L. K.

Diseases of the Endocrine Glands. By HERMAN ZONDEK, M.D. Translated by CARL P. GILES, M.D. 496 pages; 23.5 × 15.5 cm. 1946. Williams & Wilkins Company, Baltimore. Price, $11.00.

This is the fourth edition of a book which has already established itself as a valuable guide in the recognition and treatment of endocrine diseases. Dr. Zondek

has incorporated in it a majority of the developments in this field through the year 1943, and the completeness of his work is attested to by the 46 page bibliography at the end of the book. Of particular value are the numerous pictures of patients suffering from the various diseases, and the full length views emphasize the variations from normal body contour which typify a number of the endocrinopathies.

The first or general section of the book is devoted largely to the physiology and chemistry of the hormonal glands. The second or special section considers the various diseases attributable to endocrine dysfunction. In his preface, the author states that he has preferred to arrange the material according to diseases independent of their glandular origin because of the pluriglandular character of many of these disorders. In some instances this is helpful, while the understanding of other endocrine diseases would be aided by a more correlated discussion of the basic physiochemical aberrations producing the abnormalities.

This book is a valuable reference manual of endocrine disorders, and the demand which has resulted in this new edition is a tribute to its distinguished author.

J. Z. B.

Victory Over Pain. A History of Anesthesia. By VICTOR ROBINSON, M.D. 338 pages; 22 × 15 cm. 1946. Henry Schuman, New York. $4.00.

This volume, appearing on the occasion of the centenary celebration of the first administration of ether, takes its place beside a host of similar publications off the press this year. The first six chapters, devoted largely to the very early use of pain-relieving herbs, contain little that has not been well covered elsewhere. The chapters on Humphry Davy and the little-known rôle of Henry Hickman in the development of gaseous anesthesia are, however, a valuable contribution. Five chapters are devoted to Long, Wells, Jackson and Morton and the ether controversy. These are followed by an interesting section of four chapters entitled, "The Reception of the Discovery in Europe." Contributions of the famous Nicoli Ivanovich Pirogoff to the "Great Discovery" are described, especially his development of the basic idea of rectal administration of ether vapors.

The classic literature on the development and acceptance of the theory of the relief of pain by chemical agents is adequately dealt with in the following chapters on the history of the discovery of chloroform anesthesia. Two chapters are dedicated to local anesthesia (Richardson and Koller). The succeeding sections deal with the history of the development of the technics of administration of anesthetics. Only those actively engaged in the practice of anesthesiology will be greatly interested in the details of complicated apparatus and technics of administration which are described.

C. J. C.

Mongolism and Cretinism. By CLEMENS E. BENDA. 310 pages; 24 × 15.5 cm. Grune & Stratton, New York, N. Y. 1946. Price, $6.50.

Dr. Benda is the Director of the Wallace Research Laboratory for the Study of Mental Deficiency at the Wrentham State School, Wrentham, Mass. In this monograph he presents the material which he has accumulated in 10 years of intensive study of mongolism and cretinism. Throughout the various chapters which discuss the pathology and the manifestations of the two diseases, mongolism holds the dominant rôle, and the presentation of cretinism is, by the author's own statement, not intended to be complete. The possible steps to be taken from the obstetrical standpoint in the prevention of mongolism, a lengthy survey of the problem of the relation of the condition of the mother to this disease and a brief discussion of treatment complete the context of this work.

The author's views on mongolism are expressed in these statements: "Mongolism is the congenital type of hypopituitarism," and "The relationship between the mongoloid child and the pituitary dwarf is the same as that between the congenital thyroid aplastic cretin and the myxedematous child."

The prevailing view today is that mongolism is a result of a defective germ plasm and is not etiologically an endocrine dysfunction. Accordingly, the author's explanation of the disease demands closer inspection. He describes mongolism as the antithesis of acromegaly, a disease which has been shown to be due to an adenoma composed of the eosinophilic cells of the anterior lobe of the pituitary gland. The conspicuous increase in eosinophilic cells found in 54 per cent of his autopsy material he ascribes to so-called secretory stagnation, an explanation which is open to criticism. He supports his view as to the etiology of the disease by reporting good results obtained by treatment with thyrotropic hormone and thyroid substance. This method of treatment has received considerable notice recently in the lay press, and results in other clinics do not agree with the author's reports.

The chapters which discuss physical signs and symptoms and nervous and mental manifestations are instructive. The inclusion of more illustrations of the facies and other physical characteristics of the diseases would be helpful. The index is complete, and the format of the book is unusually good.

This book has already precipitated widespread discussion. Mongolism is a tragic occurrence which has darkened many lives, and there are bound to be false enthusiasms aroused by the dogmatic manner in which Dr. Benda presents his theories as to the etiology and treatment of the disease.

J. Z. B.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Hypo-Metabolism. By Esben Kirk, M.D., and Sven Ancher Kvorning, M.D. 83 pages; 24 × 15.5 cm. 1946. Einar Munksgaard, Copenhagen. Price, Dan Cr. 7.25.

The Nervous Child. Fifth Edition. By H. C. Cameron. 252 pages; 19 × 12.5 cm. 1946. Oxford University Press, New York, London.

Health Insurance in the United States. By Nathan Sinai, Dr.P.H., Odin W. Anderson, and Melvin L. Dollar, School of Public Health, University of Michigan. 115 pages; 21.5 × 14 cm. 1946. The Commonwealth Fund, New York, N. Y. Price, $1.50.

Myasthenia Gravis. By Dr. Adalberto R. Goñi. Translated by Georgianna Simmons Gittinger. 112 pages; 23.5 × 16 cm. 1946. The Williams & Wilkins Company, Baltimore.

The X-Ray Treatment of Accessible Cancer. By D. Waldron Smithers, M.D., D.M.R. Former Director Dept. Radiotherapy, St. Thomas Hospital, London. 147 pages; 27.5 × 19 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, $8.50.

Penicillin in Neurology. By A. Earl Walker, M.D., Assoc. Prof. Neurological Surgery, Univ. of Chicago, and Herbert C. Johnson, M.D. 202 pages; 24 × 14 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, $5.00.

COLLEGE NEWS NOTES

Additional Life Members of the College

The College is highly gratified to announce that the following Fellows have become Life Members:

Dr. George L. Steele, F.A.C.P., Springfield, Mass., December 18, 1946
Dr. John I. Marker, F.A.C.P., Davenport, Iowa, December 20, 1946
Dr. Lorenzo D. Massey, F.A.C.P., Osceola, Ark., December 23, 1946
Dr. Murray De Armond, F.A.C.P., Indianapolis, Ind., December 30, 1946
Dr. Joseph F. Hamilton, F.A.C.P., Memphis, Tenn., December 30, 1946
Dr. E. Cooper Cole, F.A.C.P., Toronto, Ont., Can., December 31, 1946
Dr. Felix R. Park, F.A.C.P., Tulsa, Okla., December 31, 1946
Dr. Samuel Goodman, F.A.C.P., Tulsa, Okla., January 6, 1947
Dr. Harold K. Eynon, F.A.C.P., Collingswood, N. J., January 13, 1947
Dr. William LeRoy Dunn, F.A.C.P., Washington, D. C., January 14, 1946
Dr. Evert Abram Bancker, F.A.C.P., Atlanta, Ga., January 17, 1947
Dr. Glenn Edward Drewyer, F.A.C.P., Glenwood Springs, Colo., January 17, 1947
Dr. Carl H. Fortune, F.A.C.P., Lexington, Ky., January 17, 1947
Dr. Hugh E. Kiene, F.A.C.P., Providence, R. I., January 17, 1947
Dr. Isidore Lattman, F.A.C.P., Washington, D.C., January 17, 1947
Dr. Lemuel C. McGee, F.A.C.P., Wilmington, Del., January 17, 1947
Dr. Matthew Molitch, F.A.C.P., Atlantic City, N. J., January 17, 1947
Dr. Frank F. D. Reckord, F.A.C.P., Harrisburg, Pa., January 17, 1947
Dr. Charles Windwer, F.A.C.P., Brooklyn, N. Y., January 17, 1947
Dr. Samuel C. Arnett, Jr., F.A.C.P., Lubbock, Tex., January 18, 1947
Dr. Frank C. Clifford, F.A.C.P., Toledo, Ohio, January 18, 1947
Dr. John B. D'Albora, F.A.C.P., Brooklyn, N. Y., January 18, 1947
Dr. Richard F. Herndon, F.A.C.P., Springfield, Ill., January 18, 1947
Dr. Charles W. McClure, F.A.C.P., Boston, Mass., January 18, 1947
Dr. Ernest G. McEwen, F.A.C.P., Evanston, Ill., January 18, 1947
Dr. Mary M. Spears, F.A.C.P., Philadelphia, Pa., January 21, 1947
Dr. William Stein, F.A.C.P., New Brunswick, N. J., January 21, 1947
Dr. Kenneth Taylor, F.A.C.P., New York, N. Y., January 21, 1947
Dr. Gordon B. Wilder, F.A.C.P., Anderson, Ind., January 21, 1947

The American College of Radiology and the Philadelphia Roentgen Ray Society will offer postgraduate courses in radiology, March 30–April 4, in Philadelphia. Registration is limited to 100. Preference will be given first to radiologists who served in World War II; then to qualified applicants who could not be admitted to last year's course in Philadelphia. Inquiries may be addressed to American College of Radiology, Postgraduate Courses, 20 N. Wacker Drive, Chicago 6, Ill.

The Sixteenth Annual Spring Clinical Conference of the Dallas Southern Clinical Society will occur March 17–20 in the Hotel Adolphus, Dallas. Drs. Willard O. Thompson, F.A.C.P., Chicago, and Julius L. Wilson, F.A.C.P., New Orleans, will be among the guest speakers.

The 1947 Annual Meeting of the Minnesota State Medical Association will be held in Duluth, June 30–July 2.

1947 Membership Roster Distributed

The Board of Regents authorized the publication of a complete Directory of The American College of Physicians during 1946. It became apparent subsequently that because of the scarcity of paper, and the difficulties which our printer encountered with respect to labor, the publication of a complete Directory would be exorbitant in cost and unpredictable as to date of publication. The Executive Committee of the Board of Regents therefore authorized the publication of a Membership Roster in its place. It was found that labor problems delayed the preparation and completion of this Roster so that its title has been changed to "Membership Roster—1947." The Roster has now been mailed to all members of the College in good standing. If any have failed to receive their copies, they are requested so to inform the Executive Secretary of the College. Also, it is desired that the Executive Secretary be notified of any corrections or omissions in the Roster listings.

Proposals of Candidates

In submitting the proposals of candidates for Membership in the College, it is requested that the proposers keep in mind that proposals must be filed at least thirty days in advance of action by the Committee on Credentials. This Committee will meet next on March 30 and again on April 27, 1947. A third meeting will occur at some date in the autumn of 1947. The Board of Regents will meet April 27, during the Annual Session of the College in Chicago.

Regional Meetings of the College

New England, January 28, 1947

A Regional Meeting of the College for Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont, was held at Hanover, N. H., January 28, under the general chairmanship of Dr. Harry T. French, Governor for New Hampshire, with the coöperation of Governors Alex. M. Burgess, Eugene H. Drake, Paul K. French, Chester S. Keefer, and Thomas P. Murdock. Dr. Sven M. Gundersen, F.A.C.P., was chairman of the local committee on arrangements. The program was as follows: Address of Welcome, Rolf C. Syvertsen, M.D., Dean of Dartmouth Medical School; Newer Methods of Treatment of Thyrotoxicosis, Robert H. Williams, M.D., Boston; Sympathetic Neuro Secretion and Heart Disease, Wilhelm Raab, M.D., F.A.C.P., Burlington; Interruption of the Sympathetic Nervous System in Relation to Trauma, M. Dawson Tyson, M.D., Hanover; Nutrition Problems in Medical and Surgical Practice, Charles S. Davidson, M.D., Boston; Multiple Myelomata, Herman A. Lawson, M.D., F.A.C.P., Providence; Cutaneous Diphtheria, Averill A. Liebow, M.D., New Haven; Respiratory Diseases Treated with Streptomycin, Maxwell Finland, M.D., F.A.C.P., Boston; Significance of Liver Function Tests, Franz J. Ingelfinger, M.D., Boston; Biliary Cholesterosis, Russell S. Bray, M.D., F.A.C.P., Providence; The Rôle of Endocrinology in Urology, William L. McLaughlin, M.D., Hanover; The Clinical Use of the Oximeter, John Abajian, Jr., M.D., Burlington; Objective Methods for the Evaluation of Bronchodilator Drugs in the Treatment of Bronchial Asthma, John J. Curry, M.D., Boston; The Effects of Intravenous Fluids on Plasma Volume, Hematocrit, Plasma Proteins and Urinary Output in Convalescent Patients, William J. H. Fischer, M.D., and R. O. Bowman, Ph.D., Providence; A Method of Determining the Volume of the Coronary Bed, Julius Gottlieb, M.D., F.A.C.P., Lewiston; Evaluation of the Treatment of Rheumatoid Arthritis, Marian Ropes, M.D., Boston; The Use of Sodium Succinate in the Treatment of

Acute Phenobarbital Poisoning, Richard H. Barrett, M.D., Hanover; The Morbid Interplay of Endocrines, William T. Salter, M.D., New Haven. Following a reception and banquet, Dr. David P. Barr, President of the College, addressed the members and their guests.

Eastern Pennsylvania, Southern New Jersey, and Delaware, February 7, 1947

The ninth annual round-up of College members in eastern Pennsylvania, joined by members from Delaware and southern New Jersey, took place on February 7 at Philadelphia. Governor Edward L. Bortz, assisted by Governors Lewis B. Flinn and George H. Lathrope and a committee of twenty Fellows from the area, acted as general chairman of the meeting. Distinguished guests included officers of the College and of medical schools and organizations of Philadelphia. Attendants were invited to participate during the morning in the program of the postgraduate course on Growth, Isotopes, and Tumor Formation, at the Lankenau Hospital Research Institute. The following papers by Philadelphia physicians were presented at the afternoon session: John Q. Griffith, Jr., M.D., F.A.C.P., Hypertension; Malcolm W. Miller, M.D., F.A.C.P., Anti-histamine Therapy; Louis B. Laplace, M.D., F.A.C.P., The Ageing Heart; Samuel B. Hadden, M.D., F.A.C.P., The Genesis of the Neuroses; Henry F. Lee, M.D. (by invitation), Experimental Studies with Streptomycin; Henry R. Carstens, M.D., F.A.C.P., The Medical Program for Veterans.

A reception and dinner at the Warwick Hotel followed the day's program. The meeting was a most successful one.

Virginia, February 19

An excellent program for the Virginia Regional Meeting was arranged, under the Governorship of Dr. J. Edwin Wood, Jr., by Dr. Charles M. Caravati, F.A.C.P., Richmond, and Dr. James F. Waddill, F.A.C.P., Norfolk, chairman and secretary, respectively, of the Virginia group. The meeting consisted of a scientific program in the afternoon, conducted at the McGuire General Hospital, followed by refreshments and dinner at the Richmond Academy of Medicine. The scientific papers were: Elam C. Toone, Jr., M.D., F.A.C.P., Rheumatoid Spondylitis; William B. Porter, M.D., F.A.C.P., Ductus Arteriosus: Diagnosis and Surgical Indications; Sidney G. Page, Jr., M.D. (Associate), Streptomycin in Brucellosis; T. Dewey Davis, M.D., F.A.C.P., Xanthomatous Biliary Cirrhosis; Henry St. George Tucker, Jr. (by invitation), Nitrogen Mustard in Malignant Lymphomas; Joseph R. Kriz, M.D., F.A.C.P., Reticulo-endotheliosis; J. Powell Williams, M.D. (by invitation), Liquefying Nodular Panniculitis; Wyatt E. Roye, M.D. (by invitation), Pneumoperitoneum in Tuberculosis; J. O. Burke, M.D. (by invitation), Vagotomy for Peptic Ulcer; Reno R. Porter, M.D. (Associate), Penicillin in Cardiovascular Syphilis; Benedict Nagler, M.D. (by invitation), Demonstration of Neurological Cases.

Dr. Edward L. Bortz, Vice Chairman of the Board of Governors, Governor for Eastern Pennsylvania, and Chairman of the Committee on Postgraduate Courses, and Mr. E. R. Loveland, Executive Secretary, were the guest speakers.

Dr. George Parkman Denny, F.A.C.P., Boston, formerly Colonel in the Medical Corps, A.U.S., has been awarded the Legion of Merit. Mention is made in the citation of the highest standards of medical service which were attained in hospitals of the First Service Command, to which Dr. Denny was Medical Consultant, January 1944 to October 1945.

Colonel Wesley C. Cox, (MC), USA, F.A.C.P., has been assigned to the post of Chief of the Army Industrial Hygiene Laboratory at Edgewood Arsenal, Md., with offices in the Surgeon General's office. Dr. Cox was awarded the Legion of Merit, the Army Commendation Ribbon, a Panamanian Decoration, and was named to the Order of Basco Nunez de Balboa, for his work on control of malaria in the Panama Department and Zone during the past seven years.

Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, has been awarded the Legion of Merit for "exceptionally meritorious service as commanding officer, Percy Jones General Hospital, from June 15, 1942, to April 13, 1943. For conspicuous performance as an organizer, administrator, and professional surgeon, culminating in the establishment of the country's largest Army Hospital Center, which has been unexcelled for eminent achievement in military medicine."

Edward C. Reifenstein, Jr., F.A.C.P., New York, N. Y., formerly Harvard Medical School Research Fellow at the Massachusetts General Hospital, has been appointed Research Consultant to the Sloan-Kettering Institute for Cancer Research at the Memorial Hospital Cancer Center, New York City. At the Sloan-Kettering Institute, he will carry on clinical research on the relation of glandular disturbances to cancer. He will also continue as Secretary and Editor of the Transactions of the Conferences on the Metabolic Aspects of Convalescence.

Dr. J. Robert Willson, formerly Assistant Professor at the University of Chicago, has been appointed Professor and Head of the Department of Obstetrics and Gynecology in the Temple University School of Medicine and Hospital. Dr. Valy Menkin, formerly engaged in research at the Harvard Medical School and at Duke University, has been appointed Associate Professor of Experimental Pathology.

Temple University has received from the National Cancer Institute a grant of $10,000 for a study of the relation of cellular injury to the development of repair and neoplastic tendencies, as well as a grant of $20,750 a year from the U. S. Public Health Service in support of physical and physiological studies of the heart and circulation.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to January 13, 1947 inclusive):

Robley D. Bates, Jr., Richmond, Va. (Major, MC, AUS)
Orin J. Farness, Tucson, Ariz. (Lt. Col., MC, AUS)
W. Lee Hart, Dallas, Tex. (Brig. Gen., MC, USA)
T. Haynes Harvill, Dallas, Tex. (Lt. Comdr., MC, USNR)
Ng. William Hing, Flint, Mich. (Capt. MC, AUS)
Herman Lande, New York, N. Y. (Col. MC, AUS)
Arthur G. Lueck, Des Moines, Iowa (Lt. Comdr., MC, USN)
Hertel P. Makel, Moorestown, N. J. (Col. MC, USA)
David M. Marcley, Amarillo, Tex. (Lt. Comdr., MC, USNR)
L. Tillman McDaniel, Boston, Mass. (Major, MC, AUS)
John E. Moss, Memphis, Tenn. (Lt. Comdr., MC, USN)
George P. Robb, New York, N. Y. (Lt. Col., MC, AUS)
John C. Ruddock, Los Angeles, Calif. (Capt., MC, USNR)
William G. Sauer, Rochester, Minn. (Lt., MC, AUS)
Eugene M. Schloss, Philadelphia, Pa. (Major, MC, AUS)

TENTATIVE PROGRAM
THE AMERICAN COLLEGE OF PHYSICIANS

Twenty-Eighth Annual Session

CHICAGO, ILL.

April 28–May 2, 1947

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Richard B. Capps
Lester R. Dragstedt
Frederick Fitz
Laurence E. Hines
Edwin F. Hirsch
Harry L. Huber
Sidney A. Portis
George E. Wakerlin
William L. Winters

COMMITTEE ON TECHNICAL EXHIBITS

George Morris Piersol, Chairman

Thomas Klein
Charles C. Wolferth

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Mrs. Ernest E. Irons, Honorary Chairman
Mrs. Thomas J. Coogan, General Chairman
Mrs. Grant H. Laing, Treasurer

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Mrs. Chauncey C. Maher
Mrs. Gilbert H. Marquardt
Mrs. C. Phillip Miller
Mrs. Walter L. Palmer
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Mrs. M. Herbert Barker
Mrs. Richard B. Capps
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Mrs. Laurence E. Hines
Mrs. Edwin P. Jordan
Mrs. Robert W. Keeton
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Mrs. Willard O. Thompson
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Arthur C. Bachmeyer, Director of the University Clinics, University of Chicago
Miss Mabel Binner, Director of Nursing, Children's Memorial Hospital
Mr. Edgar Blake, Jr., Administrator, Wesley Memorial Hospital
Robert Brown, Medical Director, St. Luke's Hospital
Eben Carey, Curator of Medical Exhibits, Museum of Science and Industry
Warren Cole, Assistant Dean, University of Illinois College of Medicine
Miss Henrietta Froehlke, Director of Nursing, Presbyterian Hospital
Stanley Gibson, Medical Director, Children's Memorial Hospital
R. Wendell Harrison, Dean, Division of Biological Sciences, University of Chicago
Mr. Luther Hammond, Superintendent, Passavant Memorial Hospital
Mr. Fred A. Hertwig, Warden, Cook County Hospital
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Morris Kreeger, Superintendent, Michael Reese Hospital
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Miss Mildred Lorentz, Director of Nursing, Michael Reese Hospital
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Sister Mary Therese, R.S.M., Superintendent, Mercy Hospital
Miss Madeleine M. McConnell, Director, School of Nursing, St. Luke's Hospital
Miss Veronica Miller, Superintendent, Henrotin Hospital
Mr. E. J. Millizen, Administrator, Research and Educational Hospitals
Ole Nelson, Medical Director, Cook County Hospital
Mr. Daniel Catton Rich, Director, Art Institute of Chicago
James J. Smith, Dean, Loyola University School of Medicine

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INVITATION

The City of Chicago, its medical profession, institutions and hospitals, in extending a most cordial invitation to the members of The American College of Physicians

to attend the Twenty-Eighth Annual Session, is happy indeed to offer the courtesies of the City and the facilities of its institutions to so distinguished an organization.

Chicago is the home of four Class A medical schools: (1) The University of Chicago, started through the efforts of William Rainey Harper shortly after the famous World's Fair of 1893 and located on the very territory of this Fair, is a school now internationally known, particularly recently as the place at which began the initial experiments in the atom bomb. It is the only school in Chicago which has its hospitals staffed by full-time medical men. (2) Northwestern University was begun through the efforts of Nathan Smith Davis, founder of the American Medical Association and pioneer worker in raising the standards of medical education. This school is now building a tremendous institution on the near north side within easy reach of downtown Chicago. (3) The University of Illinois, owned and operated by the State of Illinois, represents one of the finest state institutions in the country. Teaching is under the direction of men devoting all or a great share of their time to this project, buffered and complemented by a large faculty of part-time and volunteer workers. The plans of this school call for the building of several new hospitals and the steady expansion of facilities for the care of the sick of the State of Illinois. Rush Medical College, the famous school known throughout the world for its fine faculty and progressive ideas in medical education, and formerly affiliated with the University of Chicago, is now, through the Presbyterian Hospital and the Central Free Dispensary, closely affiliated with the University of Illinois so that the teaching begun in this pioneer institution which was chartered before the City of Chicago, continues as before under the watchful eye and close guidance of a great university. (4) Loyola University is located in close proximity to the great Cook County Hospital. This institution has a plan for expansion of its physical and educational plant and the building of a large hospital.

Chicago is the home of the American Medical Association, founded through the efforts of members of the faculties of Rush Medical College and Northwestern University Medical School, and of The American College of Surgeons, which continues its early efforts in raising the standards of surgical and hospital practice as it did under the inspiration of a great executive, Franklin Martin.

Chicago is the center of a tremendous industrial community. During the war her facilities were taxed to the utmost, but her hospitality was given freely and in fine measure to men of all ranks and in all branches of the Service. The Chicago Service Men's Center under the capable direction of Mayor and Mrs. Edward J. Kelly was the meeting place of huge numbers of men from the largest naval center in the World, Great Lakes, down through Fort Sheridan, the Glen View air field, Camp Grant, Navy Pier, Chanute Field, and to thousands of service men passing through the city. During the war Chicago was headquarters for the Sixth Service Command and is now headquarters for the Fifth Army.

Aside from the medical advantages and attractions of Chicago, there are other features of which this city is very proud: The Art Institute; the Museum of Science and Industry; Field Museum; Shedd Aquarium; Adler Planetarium; Chicago Historical Society; Hull House, made famous by Jane Addams; Chicago Symphony Orchestra; the Crerar Library, which is one of the largest medical libraries in the world; the "loop" with its excellent shops, stores, restaurants and theaters, and the magnificent lake front close at hand.

It is the hope of those locally responsible for the Twenty-Eighth Annual Session of the College that in accepting this invitation you will take the opportunity to visit our world famous medical and civic institutions and return home professionally and socially stimulated and satisfied that you have gained a respite from the daily duties of busy practitioners, and able to keep pace with a world that is changing almost too rapidly.

GENERAL INFORMATION

GENERAL HEADQUARTERS

Palmer House

15 E. Monroe St.

Registration headquarters, information bureau, technical exhibits, general sessions, morning lectures and panel discussions.

The Palmer House will be the headquarters hotel for Officers, Regents and Governors, and so far as facilities permit, will accommodate other members and guests of the College. Other official hotels include the Bismarck, Chicagoan, Congress, Morrison, Sherman and Stevens. A number of other hotels are also named below but none of these has officially promised accommodations.

The Congress Hotel will be the official headquarters of the technical exhibitors, who may make their reservations direct by communicating with Mr. Daniel Amico, Sales Manager.

Officers, Regents, Governors, Speakers and Clinicians on the Program should apply for hotel accommodations directly through Mr. E. R. Loveland, Executive Secretary, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa. All other physicians and guests should apply for hotel accommodations through

The Housing Committee
The American College of Physicians
c/o Chicago Convention Bureau
33 N. La Salle St.
Chicago 2, Ill.

State clearly date and time of anticipated arrival and hotel of first, second and third choice, and range of rates acceptable. A reservation card will accompany the Official Program.

PARTIAL LIST OF CHICAGO HOTELS

DOWNTOWN

Hotel	Rates* Single	Rates* Double
PALMER HOUSE 15 E. Monroe St.	3.85	5.50 up
Bismarck 171 W. Randolph St.	2.75 & 3.75	5.25
Blackstone Michigan Ave. at Balbo Ave.	4.00	7.00
Chicagoan 67 W. Madison St.	2.75	4.40
Congress 500 S. Michigan Ave.	3.50	6.00
La Salle Madison and La Salle Sts.	2.00 & 2.75	3.00 & 4.40
Morrison 79 W. Madison St.	2.75	4.40
Sherman 106 W. Randolph St.	2.75	4.40
Stevens 720 S. Michigan Ave.	3.25 up	5.00 up

* Subject to change, if OPA ceilings removed before this meeting.

NORTH SIDE

Allerton 701 N. Michigan Ave.	1.75 & 2.75	3.00 & 4.50
Drake Walton Pl. at Michigan Ave.	4.00 up	7.00 up
Edgewater Beach 5349 Sheridan Rd.	4.40 & 5.50	6.60 & 7.70
Knickerbocker 163 E. Walton Pl.	3.50	5.00

Hotel facilities are limited; members are urged to use double rooms, due to comparative shortage of single rooms. Reservations starting on Sunday, the largest checkout day, receive some preference by the hotels. Physicians should mention specifically the fact that reservations are being made in connection with the Annual Session of The American College of Physicians.

WHO MAY REGISTER—

(*a*) All members of The American College of Physicians in good standing for 1947 (dues, if not paid previously, may be paid at the Registration Bureau).

(*b*) All newly elected members.

(*c*) Senior and graduate medical students pursuing courses at the University of Chicago, University of Illinois, Northwestern University and Loyola University, without registration fee, upon presentation of matriculation cards or other evidence of registration at these institutions; exhibits, general sessions and morning lectures.

(*d*) Members of the staff, including internes, of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, general sessions and morning lectures.

(*e*) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.

(*f*) Qualified physicians who may wish to attend this Session as visitors; such physicians shall pay a registration fee of $12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

Registration Bureau—While official registration will start on Monday morning, April 28, temporary registration facilities will be open on the 4th Floor of the Palmer House on Sunday, April 27, from 2:30 to 5.00 in the afternoon. The regular Registration Bureau through the week will be open from 8:30 A.M. to 5:45 P.M.

Registration Blanks for All Clinics and Panel Discussions are sent with the program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

Bulletin Boards for special announcements will be located near the Registration Bureau on the 4th Floor of the Palmer House.

Transportation—Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the Meeting.

The General Business Meeting of the College will be held at 2:00 P.M., Thursday, May 1, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors and the annual reports will be received from the Secretary General, Executive Secretary and Treasurer. The President-Elect, Dr. Hugh J. Morgan, Nashville, Tenn., will be inducted into office.

Board and Committee Meetings—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A dinner meeting of the Board of Regents and of the Board of Governors will be held in the Crystal Room, 3rd Floor of the Palmer House, Sunday, April 27, at 7 P.M.

COMMITTEE ON CREDENTIALS

Sunday, April 27, 9:15 A.M. . . . . Room 403, 4th Floor

BOARD OF REGENTS

Palmer House, Room 9, 3rd Floor
Sunday, April 27, 2:00 P.M.
Tuesday, April 29, 12:00 M.*
Friday, May 2, 12:00 M.*

BOARD OF GOVERNORS

Palmer House, Room 9, 3rd Floor
Monday, April 28, 5:00 P.M.
Wednesday, April 30, 12:00 M.*

* Buffet luncheon served.

SPECIAL FEATURES

Monday, April 28, 1947

A SPECIAL FEATURE OF ENTERTAINMENT for everyone in attendance at the Session has been arranged by the Entertainment Committee. It will probably be the presentation of the Play, "HARVEY," starring Joe E. Brown. A special program will be announced and published later.

Wednesday, April 30, 1947

THE ANNUAL CONVOCATION OF THE COLLEGE—8:30 P.M., Grand Ballroom, Palmer House. All members of the College and their families, and those of the public who are interested, are invited. All physicians elected Fellows of the College since the 1946 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors and new Fellows to be inducted, are requested to assemble in the Red Lacquer Room, fourth floor, Palmer House, at 7:45 P.M., preparatory to the formation of the procession. They will be conducted to their seats by the Marshal of the Convocation, Dr. T. Grier Miller, promptly at 8:30 P.M. It is suggested that all appear in evening clothes

The Convocation ceremony will include the President's Address and a Convocational Oration, "Can UNESCO Succeed?" by Dr. George D. Stoddard, President, The University of Illinois, United States Delegate to the First General Conference of United Nations Educational, Scientific and Cultural Organization. The award of the John Phillips Memorial Medal for 1947 will be made and the recipients of Research Fellowships of the College for 1947 will be announced. The newly elected Fellows will be presented by the Secretary General, Dr. George Morris Piersol, and after subscribing to the Fellowship Pledge, will be inducted by the President. The President's Reception and Dance will follow immediately after the Convocation in the Red Lacquer Room. All members and their guests are requested to pass along the receiving line.

Thursday, May 1, 1947

THE ANNUAL BANQUET will be held in the Grand Ballroom of the Palmer House at 8:00 o'clock. Franklyn Price Snyder, President of Northwestern University, will be the speaker of the evening.

All members of the College, physicians of Chicago and surrounding area, visitors attending the Session, guests and friends, with their families, are cordially invited. Table reservations for groups may be arranged. Orchestral music will be furnished, and the evening has been planned as a most delightful occasion. Tickets should be purchased at the Registration Bureau by Wednesday afternoon, so that adequate preparations can be consummated.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The Ladies' Entertainment Committee has prepared an interesting program for the visiting women which it hopes will be keenly enjoyed by all. These guests are requested to register at the Ladies' Headquarters in the Ballroom Foyer, 4th Floor of the Palmer House, on their arrival in Chicago. Programs will be available at registration, as will also maps, lists of theaters, shops, restaurants and places of interest in and about Chicago.

The Ladies' Committee will be ready to start registering on Sunday afternoon, April 27. Certain of the entertainment features may be somewhat limited in accommodations and, therefore, early registration is requested.

The Ladies' Program includes a welcoming tea at the Woman's Athletic Club, a tour of the south side of Chicago along the great Outer Drive, passing by the Shedd Aquarium, Field Museum, Soldier Field, Adler Planetarium, the Midway, the campus of the University of Chicago, terminating at the Museum of Science and Industry in Jackson Park where the group will be the guests of the Director of the Museum. Buses will be provided for this tour and will leave at specified time from the Palmer House and the Stevens Hotel. The tour will be followed by a luncheon at a nearby hotel and a book review by one of Chicago's famous reviewers.

The Committee has arranged for a fashion show and breakfast at the Drake Hotel by Marshall Field and Company, and also a special exhibit-lecture-tea at the Art Institute of Chicago.

On Monday evening the women will be guests of the Local Entertainment Committee. Tuesday evening is free for theater parties or private entertainment. On Wednesday evening the Convocation will be held in the Ballroom of the Palmer House, followed by the President's Reception and Dance. On Thursday evening will be held the gala Banquet with Franklyn Bliss Snyder, President of Northwestern University, as the speaker.

THE TECHNICAL EXHIBIT will be located in the Exhibition Hall, fourth floor of the Palmer House. Exhibitors are admitted by invitation; all booths were

promptly subscribed for, some exhibitors failing to obtain space due to lateness of application.

The American College of Physicians conducts its Technical Exhibits according to the highest standards. All irrelevant products have been eliminated and only firms are invited who present a group of approved products of scientific interest to internal medicine and its allied specialties. Physicians will appreciate the difference between our Exhibit and general medical exhibits elsewhere, where frequently many products irrelevant to the actual practice of medicine are displayed and where questionable methods of selling are permitted. The College enjoys the full cooperation of its exhibitors and of its members. Exhibitors are making a special effort, under current difficult conditions, to present to the members of the College new and improved developments in their respective fields. Here, conveniently available, will be displayed the leading medical books, pharmaceuticals, apparatus and appliances, and many other products or services, making up much of the armamentarium of medical practice. These exhibitors and their displays merit your courteous attention, not only because of their educational value but because of their contributions to the support of the Annual Sessions of the College.

Special intermissions have been arranged, providing additional time for the inspection of the Exhibits.

1947 EXHIBITORS

Abbott Laboratories, North Chicago, Ill.
Allergia Coverings Co., Medway, Mass.
American Hospital Supply Corporation, Evanston, Ill.
Ames Company, Inc., Elkhart, Ind.
Appleton-Century Company, D., New York, N. Y.
Arlington Chemical Company, The, Yonkers, N. Y.
Armour Laboratories, The, Chicago, Ill.
Ayerst, McKenna & Harrison Limited, New York, N. Y.
Baum Co., Inc., W. A., New York, N. Y.
Beck-Lee Corporation, Chicago, Ill.
Becton, Dickinson & Co., Rutherford, N. J.
Bilhuber-Knoll Corp., Orange, N. J.
Blakiston Company, The, Philadelphia, Pa.
Borden Company, The, New York, N. Y.
Bristol Laboratories, Inc., New York, N. Y.
Burdick Corporation, The, Milton, Wis.
Burroughs Wellcome & Co. (U.S.A.), Inc., New York, N. Y.
Cambridge Instrument Co., Inc., New York, N. Y.
Cameron Surgical Specialty Company, Chicago and New York
Ciba Pharmaceutical Products, Inc., Summit, N. J.
Collins, Inc., Warren E., Boston, Mass.
Cream of Wheat Corporation, The, Minneapolis, Minn.
Davies, Rose & Company, Limited, Boston, Mass.
Davis Company, F. A., Philadelphia, Pa.
Devereux Schools, Devon, Pa.
Dietene Company, The, Minneapolis, Minn.
Doak Company, Inc., Cleveland, Ohio
Doho Chemical Corporation, The, New York, N. Y.
Fleet Company, Inc., C. B., Lynchburg, Va.
General Electric X-Ray Corporation, Chicago, Ill.
Gerber Products Company, Fremont, Mich.
Grune & Stratton, Inc., New York, N. Y.

Heinz Co., H. J., Pittsburgh, Pa.
Hoeber, Inc., Paul B., New York, N. Y.
Hygeia Nursing Bottle Co., Inc., The, Buffalo, N. Y.
Jones Metabolism Equipment Co., Chicago, Ill.
Kellogg Company, Battle Creek, Mich.
Kinney and Sons, Inc., H. W., Columbus, Ind.
Knox Gelatine Co., Inc., Chas. B., Johnstown, N. Y.
LaMotte Chemical Products Company, Baltimore, Md.
Lea & Febiger, Philadelphia, Pa.
Lederle Laboratories, Inc., Pearl River, N. Y.
Liebel-Flarsheim Co., The, Cincinnati, Ohio
Lilly and Company, Eli, Indianapolis, Ind.
Lippincott Company, J. B., Philadelphia, Pa.
Macmillan Company, The, New York, N. Y.
Maltine Company, The, New York, N. Y.
McNeil Laboratories, Inc., Philadelphia, Pa.
Mead Johnson & Company, Evansville, Ind.
Medical Bureau, The, Chicago, Ill.
Medical Case History Bureau, New York, N. Y.
Medical Fabrics, Inc., Paterson, N. J.
Medical Film Guild, New York, N. Y.
Medical Protective Company, The, Fort Wayne, Ind.
Merck & Co., Inc., Rahway, N. J.
Merrell Company, The Wm. S., Cincinnati, Ohio
Mosby Company, The C. V., St. Louis, Mo.
Oxford University Press, New York, N. Y.
Parke, Davis & Company, Detroit, Mich.
Patch Company, The E. L., Boston, Mass.
Picker X-Ray Corporation, New York, N. Y.
Procter & Gamble Company, The, Cincinnati, Ohio
Rare Chemicals, Inc., Harrison, N. J.
Sanborn Company, Cambridge, Mass.
Sandoz Chemical Works, Inc., New York, N. Y.
Saunders Company, W. B., Philadelphia, Pa.
Schenley Laboratories, Inc., New York, N. Y.
Schering Corporation, Bloomfield, N. J.
Searle & Co., G. D., Chicago, Ill.
Sharp & Dohme Incorporated, Philadelphia, Pa.
Smith, Kline & French Laboratories, Philadelphia, Pa.
Squibb & Sons, E. R., New York, N. Y.
Stearns & Company, Frederick, Detroit, Mich.
Swift & Company, Chicago, Ill.
Taylor Instrument Companies, Rochester, N. Y.
U. S. Vitamin Corporation, New York, N. Y.
University of Chicago Press, The, Chicago, Ill.
Upjohn Company, The, Kalamazoo, Mich.
Varick Pharmacal Company, Inc., New York, N. Y.
Walker & Company, H. W., Chicago, Ill.
Walker Vitamin Products, Inc., Mount Vernon, N. Y.
Washington Institute of Medicine, Washington, D. C.
White Laboratories, Inc., Newark, N. J.
Williams & Wilkins Company, The, Baltimore, Md.
Winthrop Chemical Company, Inc., New York, N. Y.
Wyeth Incorporated, Philadelphia, Pa.
Year Book Publishers, Inc., The, Chicago, Ill.

OUTLINE OF CHICAGO SESSION

Hotel events are indicated in **bold type**

TIME	MONDAY	TUESDAY		WEDNESDAY		THURSDAY		FRIDAY	
	April 28	**April 29**		**April 30**		**May 1**		**May 2**	
9:00 A.M. to 11:30 A.M.	Morning free. **Registration, Exhibits, etc.**	Hospital Clinics	**Morning Lectures (9:30–11:30)**	Hospital Clinics	**Morning Lectures (9:30–11:30)**	Hospital Clinics	**Morning Lectures (9:30–11:30)**	Hospital Clinics	**Morning Lectures (9:30–11:30)**
12:00 M. to 1:15 P.M.		**Panel Discussions**		**Panel Discussions**		**Panel Discussions**		**Panel Discussions**	
1:15 P.M. to 2:00 P.M.	**Luncheon**	**Luncheon**		**Luncheon**		**Luncheon**		**Luncheon**	
2:00 P.M. to 5:00 P.M.	**1st General Session**	**2nd General Session**		**3rd General Session**		**4th General Session Annual Business Meeting**		**5th General Session**	
5:00 P.M. to 8:00 P.M.	Dinner			Dinner					
8:00 P.M. to 11:00 P.M.	**Entertainment and Opening Reception**	Dinner		**Convocation,** followed by **President's Reception**		**Annual Banquet**			

GENERAL SESSIONS PROGRAM

Ballroom, Palmer House

FIRST GENERAL SESSION

Monday Afternoon, April 28, 1947

General Chairman, LeRoy H. Sloan, F.A.C.P., presiding

P.M.

2:15 **Invocation.**

His Eminence, Samuel Cardinal Stritch.

Addresses of Welcome.

The Mayor of the City of Chicago.

The Honorable DWIGHT GREEN, Governor of the State of Illinois.

MALCOLM T. MACEACHERN, F.A.C.P., President, Chicago Medical Society and Director of the American College of Sugeons.

JOSEPH L. BAER, F.A.C.S., President, Institute of Medicine of Chicago.

LAURENCE E. HINES, F.A.C.P., President, Chicago Society of Internal Medicine.

Response to Addresses of Welcome.

DAVID P. BARR, F.A.C.P., President of The American College of Physicians.

3:00 INTERMISSION.

President David P. Barr, F.A.C.P., presiding

3:20 **Physical Diagnosis.**

JAMES J. WARING, F.A.C.P., Professor of Medicine, University of Colorado School of Medicine, Denver, Colo.

3:40 **The Role of Preventive Medicine in Clinical Practice.**

WILSON G. SMILLIE (by invitation), Professor of Public Health and Preventive Medicine, Cornell University Medical College, New York, N. Y.

4:00 **The Problem of the Neurotic Patient.**

WILLIAM C. MENNINGER, F.A.C.P., Director, The Menninger Foundation; Consultant on Neuropsychiatry to the Surgeon General, U. S. Army; Member, Advisory Board to the Secretary of War; Topeka, Kans.

4:30 **Life's Situations, Emotions, and Disease.**

HAROLD G. WOLFF, F.A.C.P., Associate Professor of Medicine and Associate Professor of Psychiatry, Cornell University Medical College, New York, N. Y.

5:00 ADJOURNMENT.

8:30 o'Clock

PROGRAM OF ENTERTAINMENT

Arranged by the Chicago Committee

President's Reception

The President's Reception and Dance will follow one-half hour after this program, in the Red Lacquer Room of the Palmer House. A cordial invitation is extended to all members and guests, with their families.

FOURTH GENERAL SESSION

Thursday Afternoon, May 1, 1947

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary General, Executive Secretary and the Treasurer; elections of new Officers, Regents and Governors will take place; President-elect Hugh J. Morgan, of Nashville, Tenn., will be inducted as President and will make a brief inaugural address.

Presiding Officer

A. B. Brower, F.A.C.P., Dayton, Ohio

2:45 Origin and Physiology of Heparin.

J. Erik Jorpes (by invitation), Associate Professor of Biochemistry, Caroline Institute, Stockholm, Sweden.

3:05 The Use of Dicoumarol as an Anticoagulant.

Edgar V. Allen, F.A.C.P., Associate Professor of Medicine, Mayo Foundation; Chief of a Section, Division of Medicine, Mayo Clinic; Rochester, Minn.

3:20 A New Concept and Treatment of Purpura Hemorrhagica.

J. Garrott Allen (by invitation), Chief Surgical Resident, Albert Merritt Billings Hospital, and Instructor in Surgery, University of Chicago School of Medicine, Chicago, Ill.

3:40 INTERMISSION.

4:00 The Current Status of Folic Acid.

Carl V. Moore, Jr., F.A.C.P., Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

4:15 Nitrogen Mustard in Treatment of Leukemia and Lymphoblastoma.

Maxwell M. Wintrobe, F.A.C.P., Professor of Medicine and Head of the Department, University of Utah School of Medicine; Physician-in-Chief, Salt Lake County General Hospital; Salt Lake City, Utah.

4:30 Use of Radioactive Material in the Treatment of Blood Dyscrasias.

Leon Jacobsen (by invitation), Assistant Professor of Medicine and Associate Dean, University of Chicago School of Medicine; Attending Physician, Albert Merritt Billings Hospital; Chicago, Ill.

4:45 Specific Diagnoses and Specific Therapy in Diseases Involving the Spleen.

Charles A. Doan, F.A.C.P., Dean, Professor of Medicine and Director of Medical Research, Ohio State University College of Medicine, Columbus, Ohio.

5:00 **Chemotherapy of Multiple Myeloma.**
ISADORE SNAPPER (by invitation), Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons; Director, Postgraduate Medical Education, Mount Sinai Hospital; New York, N. Y.

5:20 ADJOURNMENT.

THE ANNUAL BANQUET OF THE COLLEGE

Thursday Evening, May 1, 1947

8:00 o'Clock

Ballroom, Palmer House

(Procure tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster: LeRoy H. Sloan, F.A.C.P., Chicago, Ill.
Address: Franklyn Bliss Snyder, President of Northwestern University

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FIFTH GENERAL SESSION

Friday Afternoon, May 2, 1947

Presiding Officer

Chauncey W. Dowden, F.A.C.P., Louisville, Ky.

P.M.

2:00 **Clinical and Pathological Comparison of Coronary Artery Disease in Different Age Groups.**
WALLACE M. YATER, F.A.C.P., Civilian Consultant, Army Institute of Pathology, Washington, D. C.

2:20 **Recent Advances in the Treatment of Cardiac Decompensation.**
EUGENE A. STEAD, JR., F.A.C.P., Professor of Medicine, Duke University School of Medicine, Durham, N. C.

2:40 **Convalescence, A Problem in Physiological Recovery.**
ROBERT W. KEETON, F.A.C.P., Professor of Medicine and Head of the Department, University of Illinois College of Medicine, Chicago, Ill.

3:00 **The Cardiac Lesions of Acute Disseminated Lupus Erythematosus.**
ELEANOR M. HUMPHREYS (by invitation), Associate Professor of Pathology, University of Chicago School of Medicine, Chicago, Ill.

3:20 INTERMISSION.

3:40 **The Management of Grand Mal and Petit Mal.**
FREDERIC A. GIBBS (by invitation), Associate Professor of Psychiatry, University of Illinois College of Medicine, Chicago, Ill.

4:00 **Human Factors in High Performance Aircraft.**
JAMES L. HOLLAND (by invitation), Captain, (MC), U.S.N., Flight Surgeon, Division of Aviation Medicine, Bureau of Medicine and Surgery, Navy Dept., Washington, D. C.

4:20 **Obesity: An Endocrine Problem.**
EDWARD H. RYNEARSON, F.A.C.P., Associate Professor of Medicine, Mayo Foundation; Consultant in Medicine, Mayo Clinic; Rochester, Minn.

4:40 **The Management of Saccular and Dissecting Aneurysm.**
LEROY H. SLOAN, F.A.C.P., Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill.

5:00 ADJOURNMENT.

MORNING LECTURES

The Morning Lectures fulfill the increasing interest in fundamental problems and are planned to supplement the subject matter of the General Sessions. The Lectures, however, are organized to give the speaker adequate time to cover his presentation fully and to utilize charts, slides, motion pictures and other media to amplify his presentation.

The Lectures will be open to all members and guests of the College.

Admission by regular registration badge; no special tickets.

Tuesday, April 29, 1947

Ballroom, Palmer House

Presiding Officer

William S. Middleton, F.A.C.P., Madison, Wis.

A.M.

9:30–10:20 **The Role of Amino Acids in Nutrition.**
WILLIAM C. ROSE (by invitation), Professor of Biochemistry, University of Illinois, Urbana, Ill.

10:20–10:40 **Intermission.**

10:40–11:30 **The Hormones of the Digestive Tract.**
ANDREW C. IVY, F.A.C.P., Distinguished Professor of Physiology and Vice President, University of Illinois, Chicago, Ill.

Wednesday, April 30, 1947

Ballroom, Palmer House

Presiding Officer

T. Homer Coffen, F.A.C.P., Portland, Ore.

A.M.

9:30–10:20 **Hypersensitivity in the Pathogenesis of Collagen-Vascular Diseases.**
ARNOLD R. RICH (by invitation), Professor of Pathology, Johns Hopkins University School of Medicine, Baltimore, Md.

10:20–10:40 **Intermission.**

10:40–11:30 **The Pathogenesis of Lupus Erythematosus and Related Conditions.**
PAUL KLEMPERER (by invitation), Clinical Professor of Pathology, Columbia University College of Physicians and Surgeons; Pathologist, Mount Sinai Hospital; New York, N. Y.

Thursday, May 1, 1947

Ballroom, Palmer House

Presiding Officer

Walter B. Martin, F.A.C.P., Norfolk, Va.

A.M.

9:30–10:20 **A Survey of Recent Developments Concerning the Concept of Coronary Disease and Its Management.**

LOUIS N. KATZ, F.A.C.P., Director of Cardiovascular Research, Michael Reese Hospital, Chicago, Ill.

10:20–10:40 **Intermission.**

10:40–11:50 **Newer Classifications and Interpretations of Hypertensive Diseases of the Retina.**

PETER C. KRONFELD (by invitation), Associate Professor of Ophthalmology, University of Illinois College of Medicine; Acting Chief of Staff, Illinois Eye and Ear Infirmary; Chicago, Ill.

Friday, May 2, 1947

Ballroom, Palmer House

Presiding Officer

T. Grier Miller, F.A.C.P., Philadelphia, Pa.

A.M.

9:30–10:20 **Clinical Pathological Correlations of Infectious Hepatitis.**

THOMAS N. HORAN, F.A.C.P., Physician, Harper Hospital, Detroit, Mich.

10:20–10:40 **Intermission.**

10:40–11:30 **Infectious Hepatitis: Clinical Manifestations and Differential Diagnosis.**

RICHARD B. CAPPS, F.A.C.P., Associate in Medicine, Northwestern University Medical School, Chicago, Ill.

PANEL DISCUSSIONS

The Panel Discussions for the 28th Annual Convention are concerned with topics of intimate interest and practical value to all members of the profession. Especially qualified men have been chosen as leaders and members of the panel personnel. These discussions will be held in the Palmer House from 12 noon to 1:15 P.M., Tuesday, Wednesday, Thursday and Friday.

Applications for tickets to Panel Discussions are to be made by members on the regular application forms accompanying the formal program. Tickets will also be available at the Registration Bureau in Convention Headquarters in the Palmer House.

Applicants may submit in writing any questions concerning any phase of the subjects in which they are especially interested. Such questions should be submitted to the General Chairman twenty-four hours before the Panel Discussion. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits.

PANEL DISCUSSIONS—Palmer House

	Red Lacquer Room 4th Floor	Crystal Room 3rd Floor	Room 14 Club Floor	Room 17 Club Floor	Room 18 Club Floor
Capacity	700	200	250	200	125
Tuesday April 29 12:00 M. to 1:15 P.M.	**I** **Electrocardiography** Moderator *Louis N. Katz, Chicago Emmet B. Bay, Chicago *Roy W. Scott, Cleveland *Frederick A. Willius, Rochester, Minn. *Frank N. Wilson, Ann Arbor	**II** **Chemotherapy** Moderator *Hugh J. Morgan, Nashville Harry Eagle, Baltimore *Chester S. Keefer, Boston Walsh McDermott, New York Irwin Peters, Chicago *Wesley W. Spink, Minneapolis *W. Barry Wood, Jr., St. Louis	**III** **Newer Aspects of the Treatment of Peptic Ulcer** Moderator *Walter L. Palmer, Chicago *Walter C. Alvarez, Rochester, Minn. *Philip W. Brown, Rochester, Minn. *Lester R. Dragstedt, Chicago *Sara M. Jordan, Boston Waltman Walters, Rochester, Minn.	**IV** **Diseases of the Liver** Moderator Frank C. Mann, Rochester, Minn. *M. Herbert Barker, Chicago *Hugh R. Butt, Rochester, Minn. *James F. Weir, Rochester, Minn. *Guy W. Wells, Providence	**V** **Renal Diseases** Moderator *Harold C. Lueth, Omaha Norris J. Heckel, Chicago *Laurence E. Hines, Chicago *Francis D. Murphy, Milwaukee Reed M. Nesbit, Ann Arbor
Wednesday April 30 12:00 M. to 1:15 P.M.	**VI** **Medical Aspects of Cardiovascular Surgery** Moderator *Paul D. White, Boston Max Minor Peet, Ann Arbor Willis J. Potts, Chicago *William D. Stroud, Philadelphia	**VII** **Psychosomatic Medicine** Moderator *William C. Menninger, Topeka Franz G. Alexander, Chicago *Henry W. Brosin, Chicago Hugh T. Carmichael, Chicago Roy R. Grinker, Chicago *Sidney A. Portis, Chicago David Slight, Chicago	**VIII** **Endocrinology, Including Diseases of the Thyroid** Moderator *Willard O. Thompson, Chicago Willard M. Allen, St. Louis Edwin B. Astwood, Boston *Elmer C. Bartels, Boston *Samuel F. Haines, Rochester, Minn. *Edward H. Rynearson, Rochester, Minn. Ephraim Shorr, New York Mayo H. Soley, San Francisco	**IX** **Myopathies** Moderator *Andrew C. Ivy, Chicago Eben J. Carey, Milwaukee Herman Chor, Chicago Abner McG. Harvey, Baltimore	**X** **Allergy** Moderator *Harry L. Huber, Chicago *Samuel M. Feinberg, Chicago *Richard A. Kern, Philadelphia *Louis E. Prickman, Rochester, Minn.

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PANEL DISCUSSIONS—Palmer House—*Continued*

Mayo H. Soley,
San Francisco

F.A.C.P.

PANEL DISCUSSIONS—Palmer House—*Continued*

	Red Lacquer Room 4th Floor	Crystal Room 3rd Floor	Room 14 Club Floor	Room 17 Club Floor	Room 18 Club Floor
Capacity	700	200	250	200	125
Thursday May 1 12:00 M. to 1:15 P.M.	**XI** **Hematology** Moderator *William B. Castle, Boston *Israel Davidsohn, Chicago *Charles A. Doan, Columbus, Ohio J. Erik Jorpes, Stockholm, Sweden *Carl V. Moore, St. Louis Edward H. Reinhard, St. Louis Isadore Snapper, New York *Maxwell M. Wintrobe, Salt Lake City	**XII** **Tumors of the Mediastinum** Moderator Jerome R. Head, Chicago Paul C. Hodges, Chicago Cecil A. Krakower, Chicago T. C. Laipply, Chicago Danely P. Slaughter, Chicago Willard Van Hazel, Chicago	**XIII** **Peripheral Vascular Disease—Anticoagulant Therapy** Moderator *Edgar V. Allen, Rochester, Minn. *Walter F. Kvale, Rochester, Minn. Karl Paul Link, Madison *Gilbert H. Marquardt, Chicago *Ovid O. Meyer, Madison Geza de Takats, Chicago *Theodore R. Van Dellen, Chicago	**XIV** **Headache** Moderator *Harold G. Wolff, New York *Bayard T. Horton, Rochester, Minn. Eric Oldberg, Chicago Lewis J. Pollock, Chicago	**XV** **Poliomyelitis** Moderator Hart E. Van Riper, New York Edward Piczak, Chicago Arthur Steindler, Iowa City Philip M. Stimson, New York Maurice B. Visscher, Minneapolis James L. Wilson, Ann Arbor
Friday May 2 12:00 M. to 1:15 P.M.	**XVI** **Cardiology** Moderator *James E. Paullin, Atlanta *Newell C. Gilbert, Chicago *William J. Kerr, San Francisco *Jonathan C. Meakins, Montreal *William D. Stroud, Philadelphia *J. Edwin Wood, Jr., Charlottesville *Wallace M. Yater, Washington, D. C.	**XVII** **Respiratory Diseases** Moderator *Francis G. Blake, New Haven *Robert G. Bloch, Chicago *Robert O. Brown, Santa Fe *Francis M. Pottenger, Sr., Monrovia *Paul S. Rhoads, Chicago	**XVIII** **Rheumatic Diseases** Moderator *Russell L. Cecil, New York *Hugo A. Freund, Detroit *Richard H. Freyberg, New York *Philip S. Hench, Rochester, Minn. *W. Paul Holbrook, Tucson *Ralph A. Kinsella, St. Louis	**XIX** **Edema** Moderator *Eugene A. Stead, Jr., Durham Norman M. Keith, Rochester, Minn. Louis Leiter, New York *Ferdinand R. Schemm, Great Falls	**XX** **Nutritional Disorders** Moderator *John B. Youmans, Chicago Paul R. Cannon, Chicago *Anton J. Carlson, Chicago *Robert W. Keeton, Chicago *Tom D. Spies, Birmingham

*F.A.C.P.

THE CLINIC SESSIONS

The Clinic Sessions—Tuesday to Friday, inclusive, from 9 A.M. to 11:30 A.M.—have been arranged at the following institutions:

A. Children's Memorial Hospital (Thursday and Friday only)

B. Cook County Hospital (two concurrent clinics daily)

C. Henrotin Hospital

D. Mercy Hospital

E. Michael Reese Hospital (three concurrent clinics daily)

F. Municipal Tuberculosis Sanitarium

G. Northwestern University Medical School

H. Passavant Memorial Hospital

J. Presbyterian Hospital (two concurrent clinics daily)

K. St. Luke's Hospital (four concurrent clinics daily)

L. University of Chicago Clinics (three concurrent clinics daily at Billings Hospital and one at Chicago Lying-in Hospital)

M. University of Illinois (one clinic daily at both the Research and Educational Hospitals and at the Neuropsychiatric Institute)

N. Veterans Administration Hospital (one clinic daily, Tuesday, Thursday and Friday, at the Chicago Institute of Medicine)

O. Wesley Memorial Hospital

Emphasis will be placed on clinics in the true sense of that word. There is scarcely a field of medicine which will not be represented on the program. In addition to the various aspects of internal medicine, there are numerous offerings in the fields of pediatrics, psychiatry, neurology, tuberculosis, psychosomatic medicine and certain surgical problems. Opportunities will be afforded for visitors to see patients at close range and observe hospital methods in Chicago.

The clinic program offers daily a capacity of over three thousand, distributed among fifteen or more of Chicago's leading medical institutions. The detailed program of clinics is not published in the ANNALS OF INTERNAL MEDICINE due to its great length and tentative state when this program is submitted for printing during January. The detailed clinic program will appear with the formal, individual program to be published during February for distribution to all members of The College and to other physicians requesting copies.

OBITUARIES

DR. CHRISTOPHER CHARLES BELING

Christopher Charles Beling, F.A.C.P., died of heart failure November 30, 1946, following an illness of about 10 weeks.

He was born in Colombo, Ceylon, April 4, 1873, educated at Wesley College where he graduated at the head of his class in 1891. He taught there for a time, then entered Ceylon Medical College, and graduated in 1897 after winning the Government Prize.

For the next two years Dr. Beling was Acting Superintendent of the Leper Asylum and acting Colonial Surgeon of the North Central Province in charge of several district hospitals. He also served as junior and senior house surgeon and physician of the Government Civil Hospital in Colombo. While there he was appointed to the British India Steam Navigation Company's *S. S. Buluwayo,* but later resigned this to take graduate work at the Royal College of Physicians and Surgeons in Edinburgh, receiving his diploma, L.R.C.P. and L.R.C.S. in January 1900.

In June of that year Dr. Beling, having come to the United States, obtained a license to practice in New York and in February, 1901, was appointed to the staff of New Jersey State Hospital for the Insane, Greystone Park, New Jersey. After six years there he took up private practice in Newark, N. J., having taken out his citizenship papers in 1905.

He was soon made a clinical assistant at the Vanderbilt Clinic, New York, under the late Dr. M. Allen Starr, and became Chief of the Neurological Clinic at the Newark City Dispensary. In 1908 Dr. Beling was placed in charge of the first psychiatric clinic in New Jersey, at St. Michael's Hospital, Newark, and held the position 15 years. He was attending neurologist at St. Michael's Hospital, and chief of the Neuro-psychiatric Department of the Newark City Hospital from 1908 to his death.

In 1917 Dr. Beling, who had been rejected for military service, became examining neuro-psychiatrist of the local and U. S. advisory draft boards, and after 1919 served four years as neuro-psychiatrist to the U. S. Public Health Service and Veterans' Bureau.

In World War II he served with local and advisory draft boards.

Dr. Beling was instrumental in founding the first Juvenile Clinic and Bureau of Mental Hygiene in Newark, was a director of the Bureau (1919–1922) and Chairman of the Committee on Juvenile Delinquency and Boys' Work of the Newark Rotary Club.

During the past 35 years Dr. Beling has been consultant in neuropsychiatry to numerous hospitals, which include: N. J. State Hospital, Greystone Park; Essex County Hospital, Cedar Grove; N. J. State Village for Epileptics at Skillman; St. Barnabas Hospital, Presbyterian Hospital, the Eye and Ear Infirmary, all in Newark; Mountainside Hospital, Montclair; West Hudson Hospital, Kearney; Hackensack Hospital; Somerset Hospital,

Somerville; Morristown Memorial Hospital; Newton Memorial Hospital; and Monmouth Memorial Hospital, Long Branch.

His society affiliations were the following: Morris County Medical Society (President 1907); Essex County Medical Society; Judicial Council of the N. J. State Medical Society 1912–46; Charter Member Academy of Medicine of Northern N. J.; New York Academy of Medicine; New York Neurological Society; first president of the New Jersey Neuro-psychiatric Association; British Medical Association; American Medical Association; American Neurological Association; American Psychiatric Association; Association for Research in Nervous and Mental Diseases; American College of Physicians (F.A.C.P., 1917). He was a Trustee of the Society for Relief of Widows and Orphans of Medical Men of New Jersey.

He contributed various articles to medical publications and was an active attendant at medical meetings. His influence was wide throughout the State and his absence will be keenly felt in many quarters. Golf, tennis, fishing, and landscape painting were his pastimes and hobbies.

He is survived by his wife, Lucille Abbott Beling; a son, Dr. Christopher Abbott Beling, whose chief interest is in neuro-surgery; and a daughter, Mrs. James A. Richardson.

GEORGE H. LATHROPE, M.D., F.A.C.P.,
Governor for N. J.

DR. EMMANUEL PERSILLIER BENOIT

Dr. Emmanuel P. Benoit, F.A.C.P., died on April 14, 1946, at his home in Montreal, aged 77 years.

Born in 1869 he qualified for his M.D. degree in 1892, and four years later became attached to the Medical Clinic of Notre Dame Hospital of which he was named chief clinician in 1908. With this Institution he was affiliated for almost half a century until his retirement in 1940.

In 1899 he succeeded to the chair of Internal Pathology at Laval University, and in 1913 was made a member of the Council of the Medical Faculty of which he was Secretary from 1929 to 1945.

In addition to the above Dr. Benoit devoted much time and energy to the organization of the nursing profession, both male and female, and their affiliation with the medical faculty.

He was Officer of the Academy, corresponding Member of the Academy of Medicine of Paris, and was one of the early Fellows of the American College of Physicians. He was also honorary member of the Medical Society of Montreal, President of the Commission of Nurses, Director of the Medical Service of the Sauvegarde Assurance Company, and Editor-in-chief of the Union Medicale from 1897–1900, and on the Editorial Staff until his death.

A skilled physician, possessed of extraordinary diagnostic acumen and wide learning, he was known also for his simplicity and modesty, his in-

tellectual vigour and integrity and withal, his ever questing spirit which his magnificent library served to gratify and at the same time to stimulate.

He leaves a wife and three sons.

A. T. HENDERSON, M.D., F.A.C.P.,
Governor for Quebec

DR. JAMES MURRAY FLYNN

Dr. James Murray Flynn, M.D., F.A.C.P., Rochester, N. Y. Born at Rochester, March 29, 1883; M.D., 1914, University of Buffalo School of Medicine; Interne, 1913–14, Buffalo General Hospital; Interne also at the Moses Taylor Hospital at Lackawanna, N. Y., and the Rochester General Hospital between 1914 and 1916; postgraduate courses in radiology taken at Cornell University and at Cook County Hospital, Chicago; practice limited to radiology since 1917; Diplomate, American Board of Radiology; served in World War I; Radiologist for many years at Rochester General Hospital, St. Mary's Hospital, Park Avenue Hospital; Consulting Radiologist, Monroe County Infirmary; Consultant in Radiology, School of Medicine and Dentistry, Strong Memorial Hospital, University of Rochester; served as former president of the Monroe County Medical Society, Rochester Academy of Medicine, Rochester Pathological Society, Seventh District Branch of the Medical Society of the State of New York, and of the Medical Society of the State of New York; Fellow and Member of the House of Delegates of the American Medical Association; Member, Radiological Society of North America and American Roentgen Ray Society; Fellow of the American College of Radiology and of the American College of Physicians, the latter since 1939; author of numerous published papers; died December 14, 1946, at the age of 63, of coronary disease and pneumonia.

Dr. Flynn was very highly respected by the members of his profession. His death is a distinct loss to the citizens and profession of Rochester, N. Y.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. GEORGE BERNARD TOPMOELLER

Dr. George Bernard Topmoeller, M.D., F.A.C.P., age 59, died October 3, 1946, at Good Samaritan Hospital in Cincinnati, after a brief illness, of gastric ulcer with recent hemorrhages. He was born in Cincinnati, Ohio, May 19, 1887. He received his early education at St. Augustine School and St. Xavier High School. Later he attended St. Xavier College. In 1910 he received his M.D. degree from the Medical College of The University of Cincinnati and entered upon a year of internship at the Good Samaritan Hospital.

Dr. Topmoeller accepted his professional responsibilities with great earnestness and conscientiousness. Never wishing to fall behind in the procession of medical progress he availed himself, at frequent intervals, of

intensive postgraduate work. In 1929 he worked in gastro-enterology at Harvard University Medical College and in 1930 in Germany. In 1936 he was elected to fellowship in the American College of Physicians and in 1937 he was made a Diplomate of the American Board of Internal Medicine. He became Chief of Staff of both Good Samaritan Hospital and St. Mary's Hospital.

In World War I he was commissioned First Lieutenant and was stationed at Camp Lee, Virginia. In World War II he devoted one day a week to the examination of recruits and served on the Board of the Procurement and Assignment Commission. He was appointed Senior Surgeon in the Reserve of the United States Public Health Service.

To quote the Cincinnati Journal of Medicine, December, 1946—"In the death of Dr. George Bernard Topmoeller we realize that our city has lost a man of exemplary character and a highly esteemed and skilled physician; that the medical profession has lost a worthy colleague who has ever been fair in all his dealings with his fellow physicians; and that the Cincinnati Academy of Medicine has lost a valuable member who was always willing to serve it to the fullest of his ability."

M. A. BLANKENHORN, M.D., F.A.C.P.,
Governor for Ohio

DR. JAMES R. E. BARNES

Dr. James R. E. Barnes (Associate), Cicero, Ill., died June 16, 1946.

He was born in 1877 and received his medical training at the Jenner Medical College, 1904.

Dr. Barnes became an Associate of the College by virtue of membership in the old American Congress on Internal Medicine, having been a charter member of that organization from 1915. When the Congress was merged with the College in 1926, Dr. Barnes became an Associate.

His death was due to cerebral hemorrhage and diabetes mellitus.

DR. ERLE BULLA CRAVEN, JR.

Dr. Erle Bulla Craven, Jr., Lexington, N. C., died June 19, 1946, following an illness of two years' duration.

Dr. Craven was born at Lexington, N. C., September 9, 1905. He held an A.B. degree from Duke University and an M.D. degree from Johns Hopkins University School of Medicine. He was an interne at Johns Hopkins Hospital and a Resident in Pathology at Duke University Hospital. Before his illness he was an Associate in Medicine, Duke University School of Medicine; Director of Laboratory, Davidson Hospital; a member of the Davidson County Medical Society, North Carolina Medical Society, and a Fellow of the American Medical Association. He had been a Fellow of The American College of Physicians since 1939, and was a Diplomate of the American Board of Internal Medicine.